2010

Approaches Towards the Synthesis of Bradyoxetin

Vanildo Martins Lima Braga

To the Graduate Council:

I am submitting herewith a dissertation written by **Vanildo Martins L. Braga** entitled "**Approaches Towards the Synthesis of Bradyoxetin.**" I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of **Doctor of Philosophy in Pharmaceutical Sciences**, with an emphasis in **Medicinal Chemistry**.

_____

John M. Rimoldi, Major Professor
Professor of Medical Chemistry

We have read this dissertation

and recommend its acceptance:

_____

Mitchell A. Avery

Professor of Medicinal Chemistry

_____

Franck E. Dayan

Adjunct Professor of Medicinal Chemistry

_____

Marc Slattery

Professor of Pharmacognosy

Accepted for the Council:

_____

Dean of the Graduate School

STATEMENT OF PERMISSION TO USE

In presenting this thesis in partial fulfillment of the requirements for a Ph.D. degree at The University of Mississippi, I agree that the Library shall make it available to borrowers under rules of the Library. Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgment of the source is made.

Permission for extensive quotation from or reproduction of this dissertation may be granted by my major professor or in his absence, by the Head of Interlibrary Services when, in the opinion of either, the proposed use of the material is for scholarly purposes. Any copying or use of the material in this dissertation for financial gain shall not be allowed without my written permission.

Signature_____

Date_____

APPROACHES TOWARDS THE SYNTHESIS OF BRADYOXETIN

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Mississippi

Vanildo Martins L. Braga

September 2010

DEDICATION

This work is dedicated to my parents, Vanildo Braga Vilela and Evany Martins L. Braga, my brother Marcos M. L. Braga and to my sister Ana Paula M. L. Braga, for their unconditional love and support through all these years.

ACKNOWLEDGMENTS

So, this is the end of the road…quite different of what I've had in mind. I've got the help of a lot of people during this process. First I would like to thank my advisor Dr. John M. Rimoldi for his patience and passion for science. For all the arrows pushing and discussions evoked in the name of organic chemistry.

My deepest gratitude to the members of my committee: Dr. Mitchell Avery, Dr. Franck Dayan and Dr. Marc Slattery. Dr. Avery will always be remembered as a great chemist, but also for his peculiar sense of humor. Dr. Dayan, from whom I've had the pleasure to develop a meaningful relationship and play guitar with. Dr. Slatery, I deeply appreciate your inputs in my defense.

Other members in this faculty were pivotal for the accomplishments in this project. My deepest gratitude to Dr. Stephen Cutler, Dr. John Williamson, Dr. Christopher McCurdy and Dr. Robert Doerksen. A very special thanks to Dr. Ronald F. Borne, for whom I've had the honor to serve as the last T.A. in Med Chem.

The list goes on, and the further it goes more personal it becomes. My deepest gratitude to all my labmates for their company in the happiness and in the misery (of course). Thanks Dr. Satish G. Puppalli, Dr. Rama Sarma Venkata S. Gadepali, Dr. Young Kim, Dr. Stephen "The Monster" Slauson, Dr. S. Anand for always being eager in engaging discussions whether in Organic Chemistry, Religion or History (yes, we've talked about a lot of stuff), as well as Indian culture. I'm very grateful to have worked side by side with Rob Smith, Sarah Scarry and Bryan Morgan. Thanks a lot to Dr. Amar Chitiboyna and so many other pos docs for their priceless input on diverse problems.

This list would never be complete without thanking The MacKenzies for their friendship during all these years. The international guest house certainly has a special place on my heart. To the friends that I've made there, Aik-Min, Josh McConn, Wesley Hatcher and Tyler Ford. Of course I'm required to talk about my fellow Brazilians. Many thanks to Paulo and Ester Carvalho (*in memorian*), for they were the first friendly faces I've met in the US. Many thanks to Dr. Cassia Mizuno and Dr. Rita Moraes, Dr. Marco Arribas and Dr. Henrique Momm.

To conclude, I would like to extend my gratitude to The Department of Medicinal Chemistry and to this outstanding University which I had the great privilege of being a part of. Thank you Ole Miss.

ABSTRACT

Quorum sensing bacteria produce and release chemical signal molecules (like N-acyl homoserine lactones, AHL) that increase in concentration as a function of cell density. The responses cover a large spectrum of process such as the virulence in *Staphylococcus aureus*, competence for DNA-uptake in *Bacillus subtilis* and *Streptococcus pneumoniae*, sporulation in *Bacillus subtilis*, conjugal plasmid transfer in *Enterococcus faecalis*, and bacteriocin production in lactic acid bacteria. The collapse of (AHL) signaling system in bacteria represents an attractive therapeutic approach towards the development of new antibiotics. Recently, a new extracellular modulator was isolated from a symbiotic bacterium (*Bradyrhizobium japonicum*) that nodulates soybean. This quorum sensing molecule, containing a novel oxetane ring, was partially characterized and named bradyoxetin (2-{4-[[4-(3-aminooxetan-2-yl)phenyl](imino)methyl]phenyl}oxetan-3-ylamine). The objective of this dissertation research was to confirm the absolute stereochemistry of bradyoxetin by total synthesis, with the production of the four possible stereoisomers. Novel chemical strategies for the efficient formation of oxetane rings were developed, using the inexpensive chiral drug chloramphenicol as a starting material. Employing a five-step protocol, suitable oxetane intermediates were synthesized and characterized as precursors to the final step of bradyoxetin synthesis. Approaches towards the synthesis were also developed for the construction of the natural product oxetin. New scaffolds bearing an oxetane ring were created for the future development of new antibiotics.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

SCHEME PAGE

CHAPTER 1: QUORUM SENSING

1.1 Introduction to Quorum Sensing

There is a global consensus that a part of the microbial world that was once "under a limited control" is now at the edge of a mass rebellion. The drug arsenal once used to control diseases caused by pathogenic bacteria genera such as *Staphylococcus*, *Mycobacterium* and *Streptococcus* have become in many instances useless. Bacteria have acquired resistance to antibacterial drugs by a variety of mechanisms which include, but are not limited to, the increased ability to degrade anti-bacterial compounds through β-lactamases (Mansour et al., 2008), decreased permeability (Kumar & Schweizer, 2005), decreased affinity for antibiotics (Zapun et al., 2008), and increased efflux (Xian-Zhi & Nikaido, 2009) of antibiotics which leaves us with the option of discovering new drugs or developing new strategies to circumvent the resistance problem.

Cellular communication, whether among nerve cells, or bacteria, happens through the complex use of signaling molecules that govern basic cellular activities and coordinating cell actions, representing a reasonable target for drug discovery. In bacteria, the organization and coordination resembles multi-cellular organisms (Bassler & Losick, 2006; Ben-Jacob & Levine, 2006) and is referred to as "quorum sensing" (Hentzer & Givskov, 2003). Before a necessary and drastic change in the environment occurs there must be a minimum concentration of a bacterial population, therefore termed, a quorum. The size of the population is sensed by the individuals; in this particular case the cells, through chemical signaling. Therefore, the signals used in bacterial language are small molecules, sometimes referred as auto-inducers (AIs) (Pomianek & Semmelhack, 2007),

or pheromones (Kleerebezem, 1997) released into the environment where they grow (Figure 1). Examples of such molecules include acyl-homoserine lactones (**1**-**2**) (Parsek and Greenberg 2000), diketopiperazines (**3**-**4**) (Holden et al., 1999), quinolones (**5**) (Pesci et al., 1999), γ-butyrolactones (**6**-**7**) (Chun et al., 1997; Hentzer et al., 2002; Manefield et al., 2002) and surprisingly a borate (**8**) (Xin et al., 2002).

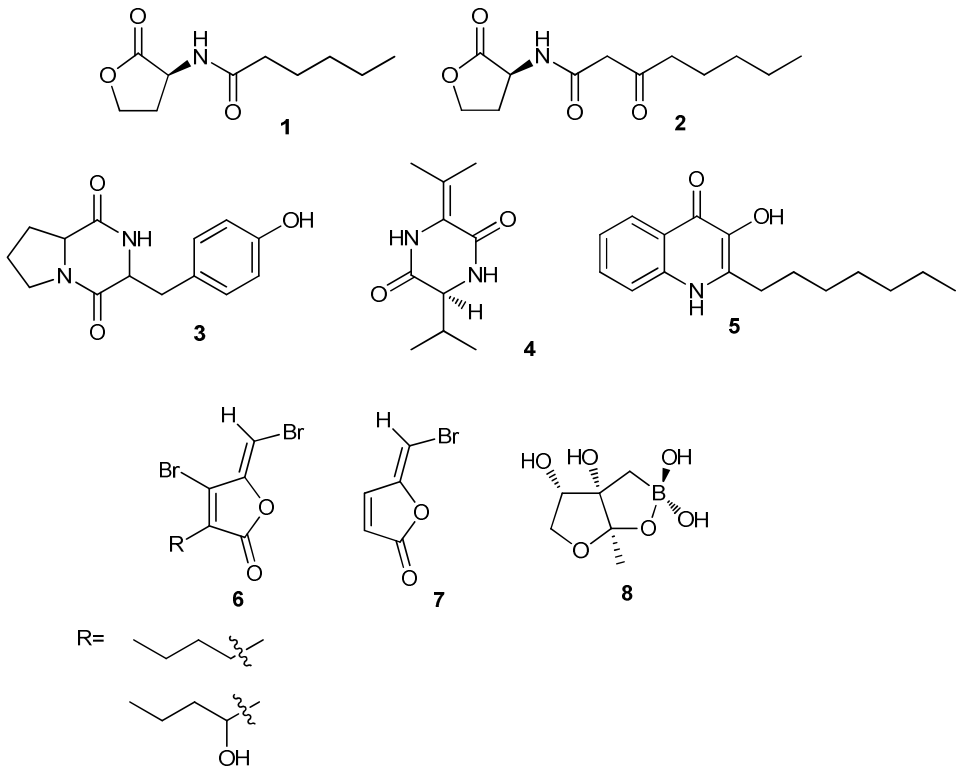


Figure 1. Autoinducer chemotypes.

When the concentration of autoinducers reaches a threshold level perceived by the population, it is said that the population is "quorated" (Telford, 1998), which implies that

there is a significant number of individuals able to make a behavioral group-base decision (de Kievit, 2000). The molecules have to travel either from one cell to another to implicate an effective change; cross the cell surface through active transport (Pestova et al., 1996) or passive diffusion, and reach a different cell. The signal producing proteins in Gram-positive bacteria are membrane embedded proteins responsible for a double task, namely production and secretion of chemical signals (Ishii, 2010). In Gram-negative bacteria the cytosolic type Lux-I protein has been identified and belongs to the most common and studied route (Williams, 2007).

Once inside the cell, the signal will have to interact with a receptor which will convert the chemical signal into information. This “chemical data” will most likely end up as a “genetic instruction” or expressed gene. Different species tend to use different sets of molecules for different tasks, but one set of molecules can have antagonistic or agonistic response in different species of bacteria. In the previously cellular scenario described above there are places for agonistic and antagonistic events. Both can be used to elicit a desirable therapeutic response. The interventions can be summarized in seven categories: i.) inhibition of auto inducer synthesis; ii.) auto inducer receptor antagonism; iii.) inhibition of targets downstream of receptor binding; iv.) sequestration of auto inducers by antibodies; v.) degradation of auto inducers performed by either enzymes or catalytic antibodies (abzymes); vi.) inhibition of auto inducer transport/secretion and; vii.) antagonism of autoinducer’s receptors.

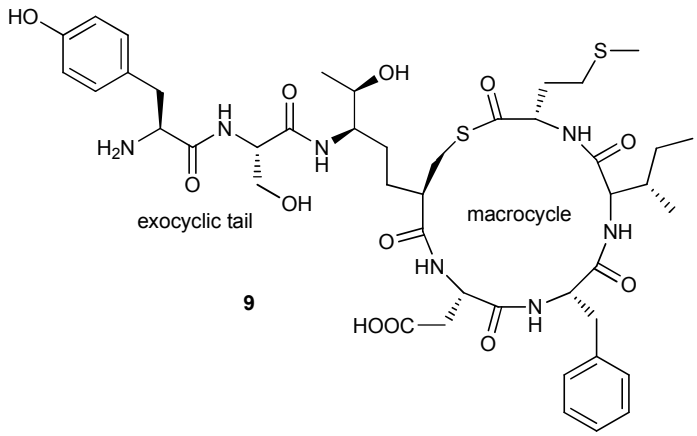
Although it is widely believed that quorum sensing has an impact on cellular activity, it is not necessary for bacterial survival *per se*. It can be very useful as an adjuvant therapy but quorum sensing molecules lack bactericidal and/or bacteriostatic

activity. Quorum sensing been implicated in a wide variety of changes in phenotypes including: secretion of virulence factors (Dong et al., 2001; Lyon & Muir, 2003; Jones et al., 2005), biofilm formation (Hentzer et al., 2003; Kaufmann et al., 2006), bioluminescence production (Dunlap, 1999; Frezza et al., 2007), conjugation (Vannini et al., 2004), sporulation (Varga, 2004), expression of virulence factors (Harraghy et al., 2007), swarming motility (Gonzalez Barrios et al., 2006) and symbiosis (Rumbaugh, 2007).

1.2 Quorum Sensing Pathways and Inhibitors

In order to have a better understanding of how quorum sensing can be used to manipulate bacterial behavior, it is critical to have a better understanding of quorum sensing pathways. There are three pathways that describe interactions among bacteria: 1.) the autoinducer peptide (AIP) quorum sensing pathway, 2.) the acyl-homo-serine lactone (AHL) quorum sensing pathway and 3.) the autoinducer 2 (AI-2) pathway.

The AIP pathway is the most common type of quorum sensing pathway among Gram-positive bacteria. The chemical signals used are oligopeptides, which are structurally limited to 5-17 amino acids residues and are usually modified post-translationally with diverse cyclic structures including thiolactones (**9**) (Mayville et al., 1999; McDowell et al., 2001), lanthionine (e.g., nisin or subtilin) (Kies et al., 2003; Kleerebezem, 2004; Dufour et al., 2007) or isoprenyl groups, as in the case of the unique ComX pheromone (**10**) from *Bacillus subtilis* (Ansaldi et al., 2002). These functionalities are thought to provide binding selectivity and signal specificity in Gram- positive bacteria (Figure 2).



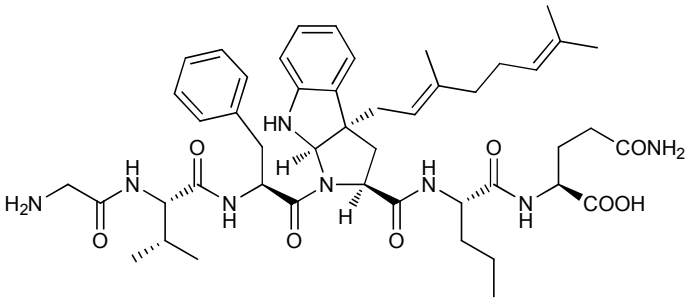


Figure 2. Diverse AIPs: Thiolactones from *Streptoccocus aureus*, and isoprenoidal ComX from *Bacillus subtillis*.

The AIPs start their cycle by binding to a receptor on the bacterial surface which is part of the two component adaptive system for the detection of autoinducers. These two component systems are composed of a sensor and a response regulator protein which utilizes phosphorylation for signal status. If the AIP is bound to a receptor, phosphorylation of the histidine sensor kinase protein (letter H-Figure 3) occurs. A second event uses the phosphoryl group of the histidine kinase for the phosphorylation of a conserved aspartate residue (letter D-Figure 3) of a response regulatory protein. The response regulatory protein is involved in the synthesis and release on the AIPs, forming

a feedback loop control and the expression of number of genes which leads to quorum sensing phenotypic responses. The exporting of the AIPs is performed through active transport using ATP-binding cassettes (ABCs) which are also responsible for the processing of the peptide-pheromone precursors (Ishii, 2010). Once transported out of the cell, the peptide-pheromones can interact with another cell or be used by the same cell initiating the cycle again.

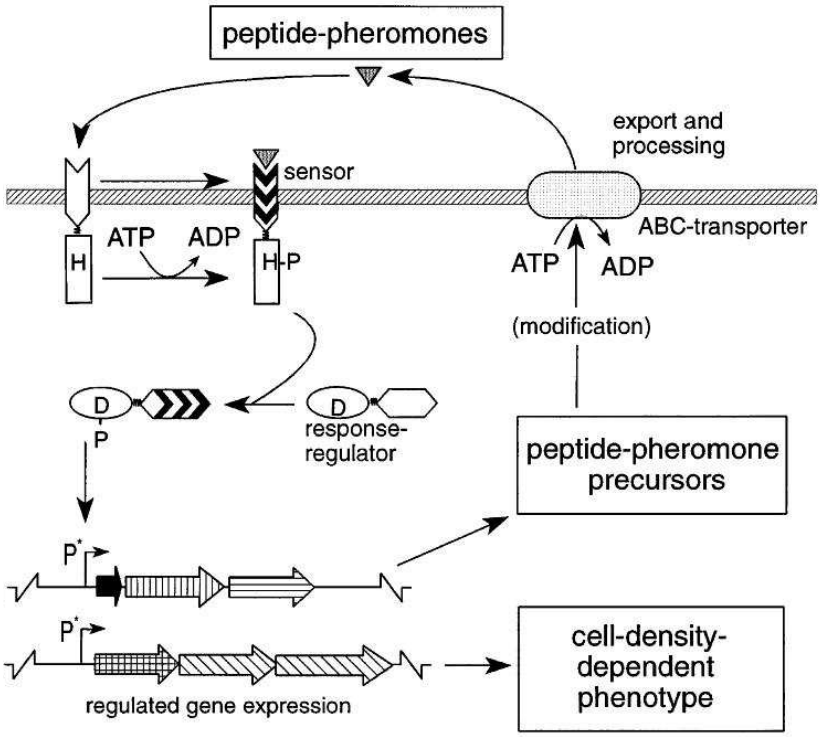


Figure 3. Model of quorum sensing that involves peptide pheromones and a two component system in Gram-positive bacteria (Kleerebezem, 1997). (Permission granted for reproduction).

The other Gram-positive bacteria quorum sensing system have minor, but important modifications, including the addition of an accessory gene regulatory system

(Agr) (Peng, 1988). Examples are found in *S. aureus* and also identified in Agr-like gene system (AgrF or Fsr) in *E. faecalis* (Qin et al., 2000). These bacteria still possess protein histidine kinase (designated as AgrC in *S. aureus* (Lina et al., 1998) and FsrC in *E .faecalis* (Qin et al., 2000) but use different peptide export proteins instead of the ABC proteins. Additionally, AgrA (Koenig et al., 2004) is the response regulator and AgrD (McDowell et al., 2001) is the protein responsible for the AIP production. AgrB (Zhang et al., 2002; Qiu et al., 2005) is the protein responsible for the modification of the peptide produced by AgrD (Zhang et al., 2004) and secretion of the modified peptide to the medium (Figure 4).

These two systems have gained extra attention since *S. aureus* and *S. epidermidis* are the main causes of nosocomial infections. It is known that the locus *agr* is a global regulatory gene and hence responsible for a number of virulence factors (Ji et al., 1995). In *S. aureus* the strains are categorized into four *agr* subgroups. The expression of each of these *agr* genes can inhibit other pathways (Jensen et al., 2008).

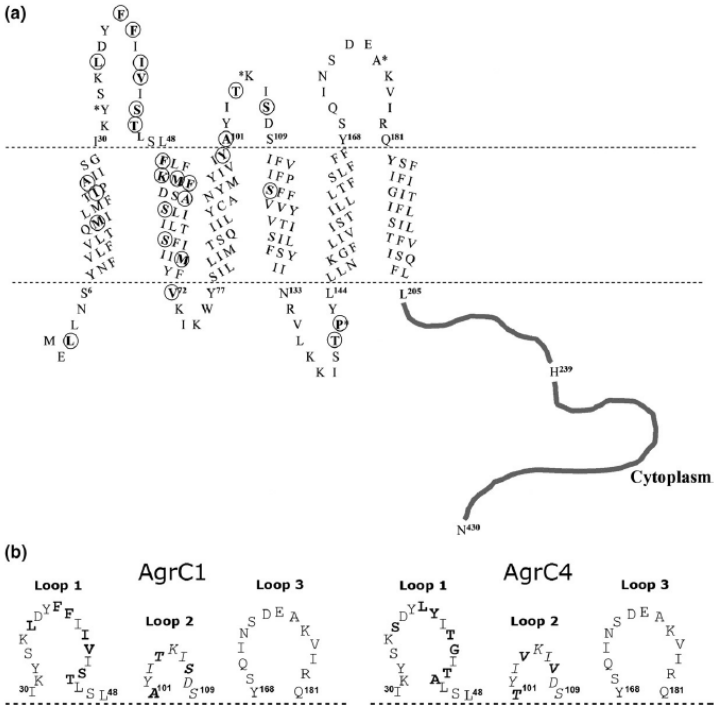


Figure 4. Structural differences in AgrCs of *Staphylococcus aureus* (Jensen et al., 2008) (Permission granted for reproduction).

Based on the pathways described, it is feasible to propose that the inhibition of key points in the biochemical pathway of quorum sensing could elicit a shutdown of the system, provoking a desirable therapeutic effect. Select AIP targets may include: i.) antagonism of AIP receptor; ii.) histidine protein kinase inhibitors; iii.) inhibition of phosphoryl transferases from the His residue to the Asp residue of the response regulator; iv.) inhibition of the enzymes responsible for the AIP synthesis and/or post-translational modification and; v.) inhibition of efflux transporters responsible for AIP effusion across membrane.

1.3 Histidine Protein Kinase Inhibitors

Patients with cystic fibrosis are likely to suffer from pulmonary infections. A common pathogen involved in such infections is *Pseudomonas aeruginosa* (Roychoudhury et al., 1993) which synthesizes the ex-polysaccaride coat alginate thus rendering the access of bactericidal drugs to the correspondent site of action a difficult task. The genes involved in alginate production are part of a two component system regulated by AlgR2/AlgR1. Histidine kinase AlgR2 is inhibited by compounds **11** and **12** while inhibitor **13** was reported to interfere with the DNA binding activity responsible for the response regulator AlgR1. Inhibitors **13** and **14** also act on a broader spectrum of histidine kinases such as CheA, NRII, KinA and VirA (Figure 5).

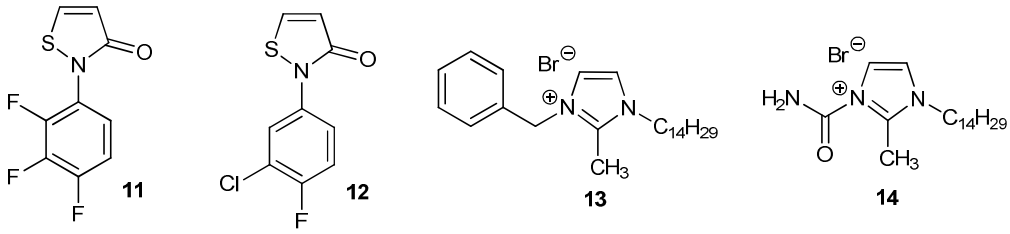


Figure 5. Histidine protein kinase inhibitors.

A zerumbone analog **15**, Figure 6, (Yamamoto et al., 2001) inhibited the histidine kinase of YycG on *Bacillus subtilis* (Kitayama et al., 2004). Additional zerumbone analogs were synthesized (e.g., tryptophan analog **16**) and found to be equipotent with **15** (Kitayama et al., 2007). Several analogs also exhibited activity against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecalis* (VRE).

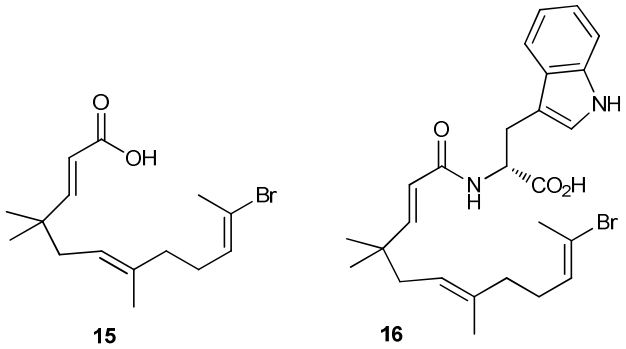
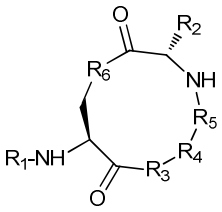


Figure 6. Zerumbone histidine kinase inhibitors.

1.4 AIP Antagonists

In 1995, it was demonstrated that the virulence factors in *S.aureus* were controlled by a cell density system that made use of an octapeptide produced by the bacterium itself. The study also revealed that this octapeptide activated the expression of the *agr* locus; the octapeptide sequence was determined to be YSTCDFIM (Ji et al., 1995). The peptide was purified, characterized and synthesized but had no detectable activity. Evaluation of the mass spectrometry data suggested that this synthetic peptide was dimeric and its mass included a neutral loss of water. When interpreted as a whole, this led the authors to suggest that the cysteine in the synthetic peptide was oxidized to a disulfide and the natural isolated pheromone contained a cyclic thioesther introduced post-translationally. The hypothesis was confirmed by treatment of the native peptides with iodoacetic acid and hydroxylamine. Iodoacetic acid failed to react with the peptide (as evidenced by no free SH groups), while hydroxylamine reacted with the putative thioester, yielding a product that lacked biological activity (Ji et al., 1997).

Additional insights were acquired through structure-activity relationship studies with a series of analogs synthesized to determine key residues that are involved in agonistic or antagonistic activity (Table 1). Conclusions were drawn from these studies that demonstrated the sulfur atom, when oxidized, abolishes biological activity. Also when the methionine was replaced with norleucine, serine, glutamic acid, lysine or proline, no activity was observed (McDowell et al., 2001).



Comp.	R1	R2	R3	R4	R5	R6	IC_{50}	ED_{50}
AIP-1	H-Tyr-Ser-Thr	$CH_2CH_2SCH_3$	Asp	Phe	Ile	S	-	19 nM
	H-Tyr-Ser-Thr	$CH_2CH_2SOCH_3$	Asp	Phe	Ile	S	-	-
	CH_3CO	$CH_2CH_2SCH_3$	Asp	Phe	Ile	S	8 μM	-
AIP-II	Gly-Val-Asn-Ala	$CH_2(C_6H_5)$	Ser	Ser	Leu	S	2 nM	-
	CH_3CO	$CH_2(C_6H_5)$	Ser	Ser	Leu	S	4 μM	-
	H-Tyr-Ser-Thr	$CH_2CH_2SCH_3$	Asp	Phe	Ile	NH	-	24 μM
	H-Ala-Ser-Thr	$CH_2CH_2SCH_3$	Asp	Phe	Ile	S	-	161 nM
	H-Tyr-Ala-Thr	$CH_2CH_2SCH_3$	Asp	Phe	Ile	S	-	9 nM
	H-Tyr-Ser-Ala	$CH_2CH_2SCH_3$	Asp	Phe	Ile	S	-	248 nM
	H-Tyr-Ser-Thr	$CH_2CH_2SCH_3$	Ala	Phe	Ile	S	33 nM	-
	H-Tyr-Ser-Thr	$CH_2CH_2SCH_3$	Asp	Ala	Ile	S	-	9 μM
	H-Tyr-Ser-Thr	$CH_2CH_2SCH_3$	Asp	Phe	Ala	S	-	11 μM
	H-Tyr-Ser-Thr	CH_3	Asp	Phe	Ile	S	-	9.5 μM

Table 1. Structures and activities of diverse AIPs.

The most compelling changes were achieved when alanine was introduced in the place of aspartic acid on the cyclic structure, which changed the nature of the peptide from an activator, with ED_{50} of 19 nM, to an inhibitor of toxic shock syndrome toxin (TTST-1) and enterotoxin C-3, with an IC_{50} of 33 nM. D-Amino acids were also part of the study and analogs of AIP-1 replacing the L-amino acid residue for the D-isomer were

tested. In the case of activation, the activity was reduced for most of the analogs with the exception of D-Phe and D-Met.

An SAR study performed with AIPs revealed that for *S. aureus*, a common template was able to antagonize AgrC: TrAIP-II (Mayville et al., 1999). The SAR study revealed important details about the interaction between the peptides produced by AgrD and the receptor AgrC such as: (i) the amino acid sequence and the stereochemistry of the AIP are critical for the interaction between the peptide and its receptor; (ii) inhibition of *agr* expression is undermined if either the amino acid sequence or stereochemistry is altered, but not when the changes concern the chemical reactivity of the cyclic linkage. The synthesis of the peptides used in the SAR study was performed using solid-phase protocols.

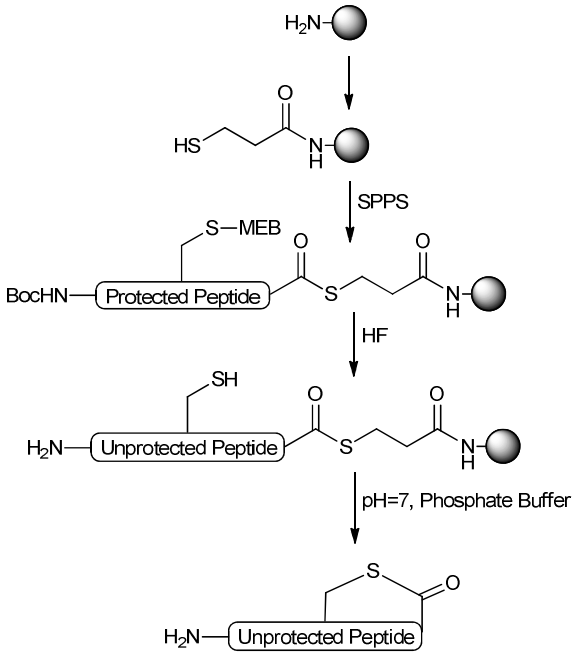


Figure 7. Synthesis of *S. aureus* AIPs (Mayville et al., 1999)

The study also proposed that AIPs of the same *S. aureus* class bind differently from AIPs of different *S. aureus* types. On an intraclass association, side chain interactions would increase the specificity leading to an adjustment that would position the thiol ester linkage of the peptide next to a nucleophilic group embedded on AgrC. Therefore a covalent bond between AgrC and the the AIP would be formed, imparting conformational changes on the receptor resulting in the histidine kinase to suffer trans-phosphorylation through dimerization (Cisar et al., 2009). The aforementioned events would lead to the activation scenario and therefore to signal-transduction and expression of *agr*. Regarding the interclass receptor-ligand scenario, there would not be a nucleophilic attack due to the non-aligment provided by the absent side-chain interactions. Therefore a non-covalent binding interaction would take place and no signal-transduction would be possible leading to the antagonistic thread (Figure 8).

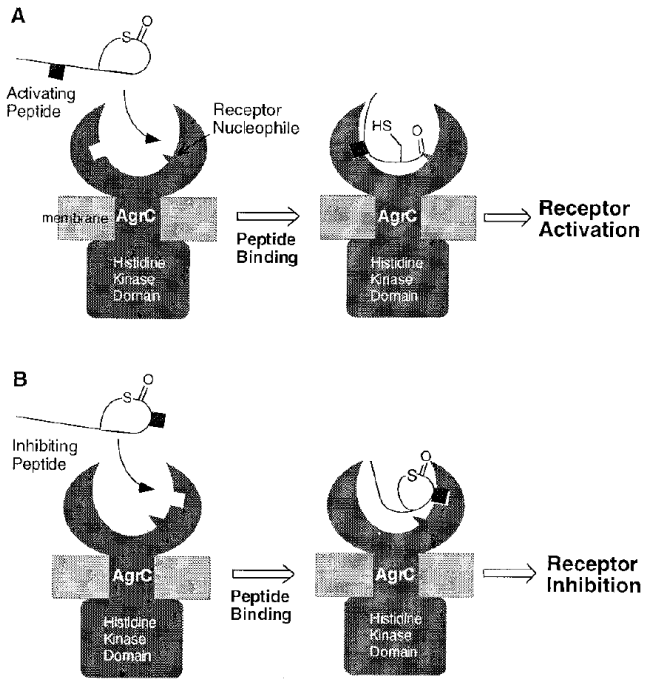


Figure 8. Proposed model for agonism and antagonism of AgrC (Mayville et al., 1999). (Figure reproduced with permission).

It was hypothesized that the peptide side chain (sometimes referred as the tail) bound to the thiolactone has a fundamental role for the activation of the AgrC receptor-histidine kinase, as well as for defining the agonistic/antagonistic nature of the AIP. With this in mind, a second SAR study was conducted involving chimeric receptors and diverse AIPs (wild and synthetic) from a variety of *Staphylococcus* species. The test of the chimeric receptors against a number of AIP analogs localized the primary ligand recognition site to the receptor distal subdomain and revealed that the AIPs bind primarily to a putative hydrophobic pocket in the receptor (Figure 9). This interaction is driven in part by a highly hydrophobic moiety on the AIPs which proved to be essential for self- activation as well as for cross-inhibition (Wright et al., 2004).

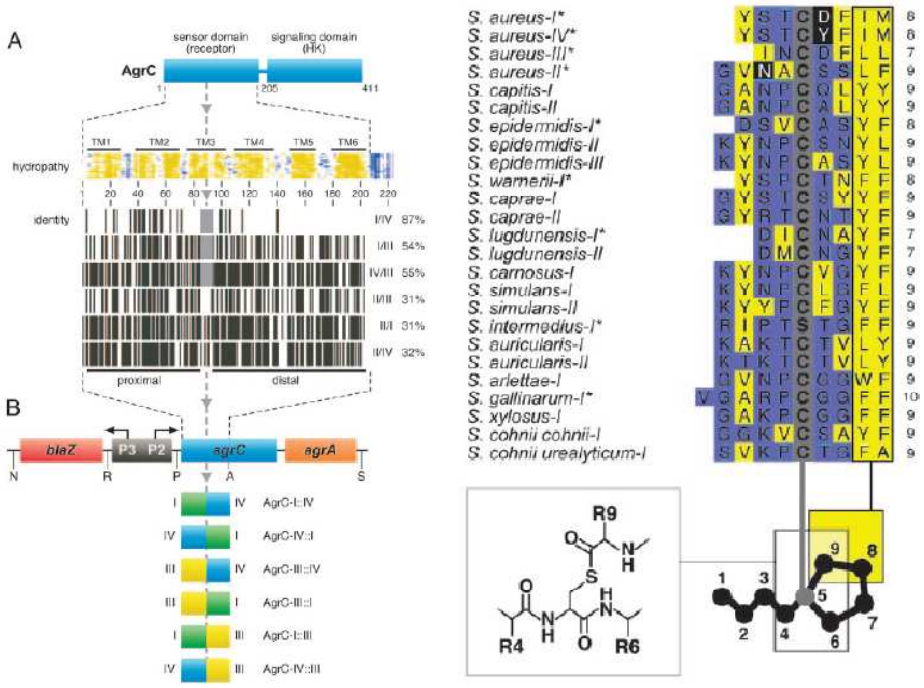


Figure 9. Strategy used to generate chimeric AgrC and alignment of wild AIPs from different *Staphiloccocci* showing the highly conserved amino acids 9 and 8 as well as the cysteine residue (Wright et al., 2004). (Figure reproduced with permission).

The study determined several intrinsic aspects of the AIP-AgrC interaction: i.) the distal region of the AgrC domain contains the primary elements involved for activation; ii.) the specificity for the activation in the AIP can be accounted to D5 and Y5 (Figure 9) on AIP-I and AIP-IV, respectively, in the macrocycle ring adjoining the conserved cysteine; iii.) the proximal domain of the receptor confers a secondary role in ligand cross-reactivity presenting the ability to react to noncognate AIPs; iv.) a massive hydrophobic residue, conserved on all *Staphylococcus* AIPs seems to be a key component for AgrC-AIP binding.

The ligand-binding event of AgrC-AIP is expected to generate conformational changes in the AIP and/or the AgrC receptor for activation. It is also important to note that the chimeric receptors can be of critical importance in the study of interactions between ligand and receptor (Figure 10).

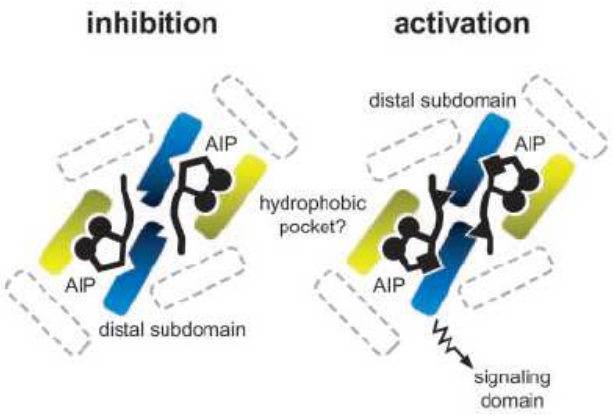


Figure 10: activation and inhibition of AgrC. The binding is driven by the hydrophobic patch (two circles) into the hydrophobic binding pocket (shaded in yellow). (Wright et al., 2004). (Figure reproduced with permission)

An interesting SAR study was recently reported, in which 10 analogs of trAIP-II (**17**) were synthesized (George et al., 2008). Since compounds lacking the side chain would present an inhibitory effect, they were tested against AgrC-II to investigate the cognate effects and against AgrC-I for the non-cognate effects. The following conclusions were made based on the study: (i) regarding cognate and non-cognate inhibitory effect, both groups have similar tendencies; (ii) from the compounds that have measurable activities it was observed that the antagonism for the non-cognate receptor (AgrC-I) was stronger than of the cognate-receptor (AgrC-II); (iii) a main pharmacophore group for *agr* antagonism in trAIP-II was improved. One half of the molecule including

cysteine and two terminal hydrophobic residues are critical for activity. The remainder of the molecule seems to be non-essential as shown in Figure 11.

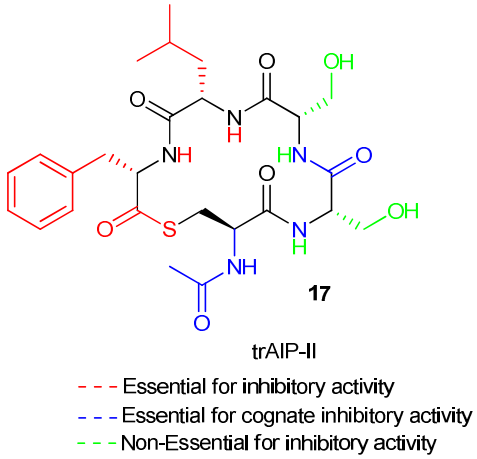


Figure 11. Proposed pharmacophore model for trAIP-II.

Other AgrC antagonists were discovered in a unique SAR study involving AIP-1(**18**) and AIP-2 (**19**). Some issues were considered in designing the features for AgrC antagonists: (i) two amino acids in the macrocycle are essential for the interactions of AIP-1 and AIP-2 with their respective cognate receptors, $Phe^{6}Ile^{7}$ (in AIP-1) and $Leu^{8}Phe^{9}$ (in AIP-2); (ii) the substitution of the aminoacid vicinal to the highly conserved cysteine (Asp^{5} for AIP-1 and Ser^{6} for AIP-2) for an Ala residue resulted in a powerful AgrC competitive antagonist (Mayville et al. 1999; McDowell et al., 2001; Lyon et al., 2002). Indeed, (Ala^{5})AIP-1 (Figure 12) is a potent inhibitor on all *S. aureus* AgrCs with IC_{50} values ranging between 0.3 and 21 nM; (iii) analogs lacking the exocyclic tail are weak antagonists although the exocyclic tail seems to have an impact on the macrocyclic "address" affinity. ^{1}H-NMR studies were performed on the (Asp^{5}) AIP-1 analog. The hydroxy belonging to Ser^{2} and Thr^{3} revealed a doublet at δ 4.95 and a triplet at δ 5.24

while the hydroxyls for AIP-1 revealed two broad singlets. This implied that the hydroxy groups in (Asp^5)AIP-1 are solvent shielded with a very slow rate of exchange. Therefore it was proposed that a substitution of Asp^5 for an Ala residue would provoke minor changes in the macrocyclic conformation but would induce critical adjustments in the exocyclic tail culminating in an affinity increase (Chan et al., 2004).

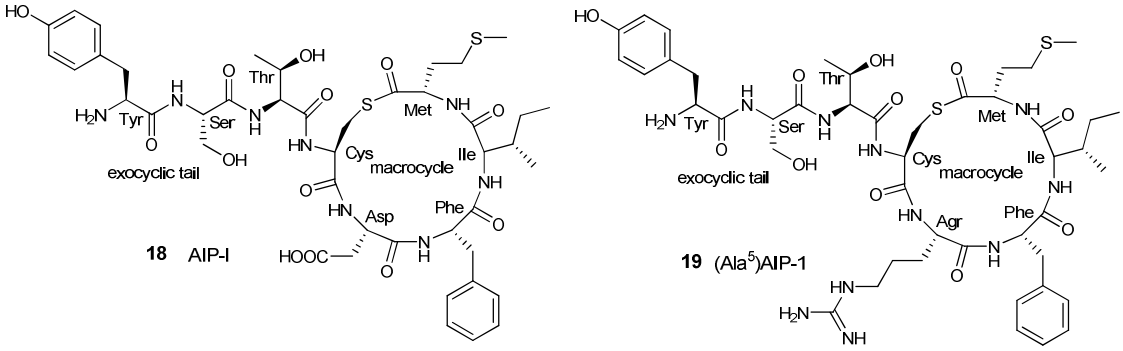
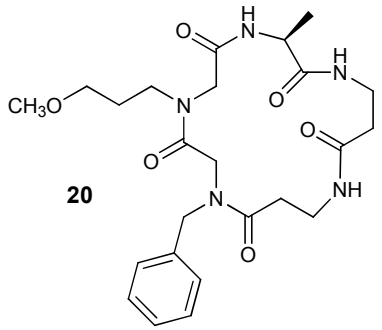


Figure 12. AIP-1 and (Ala^5)AIP-1.

Based on (Ala^5)AIP-1 an additional set of analogs were synthesized and evaluated. The replacement of Asp^5 by Ala did not affect activity. The replacement of Tyr^1 by biphenyl moieties had an impact on the affinity for AgrC-1, but not for AgrC-2.

Biostability is always an issue when one considers drug design strategies (Grabley, 1999). With this in mind, *N*-substituted glycines oligomers, or peptoids, have been shown to be valuable peptide mimetics due to their high stability and relative ease of synthesis (Patch, 2004). Additionally, many biologic phenomena have been reported to be probed by peptoids (Hara et al., 2006; Xiao et al., 2007).

Peptomers (peptide-peptoid hybrids) (Østergaard & Holm, 1997) were proposed as feasible mimetics for AIP-1, following the logic of previous SAR works (Fowler et al., 2008). A series of peptomers were tested and it was discovered that one of them was able to *stimulate* bio-film formation, presenting an agonistic role in *S. aureus* quorum sensing (Figure 13).



20

Figure 13. Peptomer with biofilm stimulatory activity on *S. aureus*.

Recently antibodies were used as AIP antagonists (Park et al., 2007). Initial focus centered on the AIP-4 QS system and its cognate strains RN4850 and NRS168 (Lyon et al., 2000). The hapten AP-4 (**21**) was designed with a major concern in mind, replacement of the native thiolactone for a lactone-containing hapten in order to improve aminolytic stability (Shigenaga & Janda 2006). This strategy prevented any structural change during the immunization process therefore averting the production of compounds generated due to degradation haptens (Kaufmann et al., 2005), as well as a possible intra molecular thiol exchange. The antibody was obtained through the immunization of mice after synthetic AP4-hapten 5 (**22**) was conjugated with carrier proteins keyhole hemocyanin (KHL) and bovine serum albumin (BSA) (Figure 14).

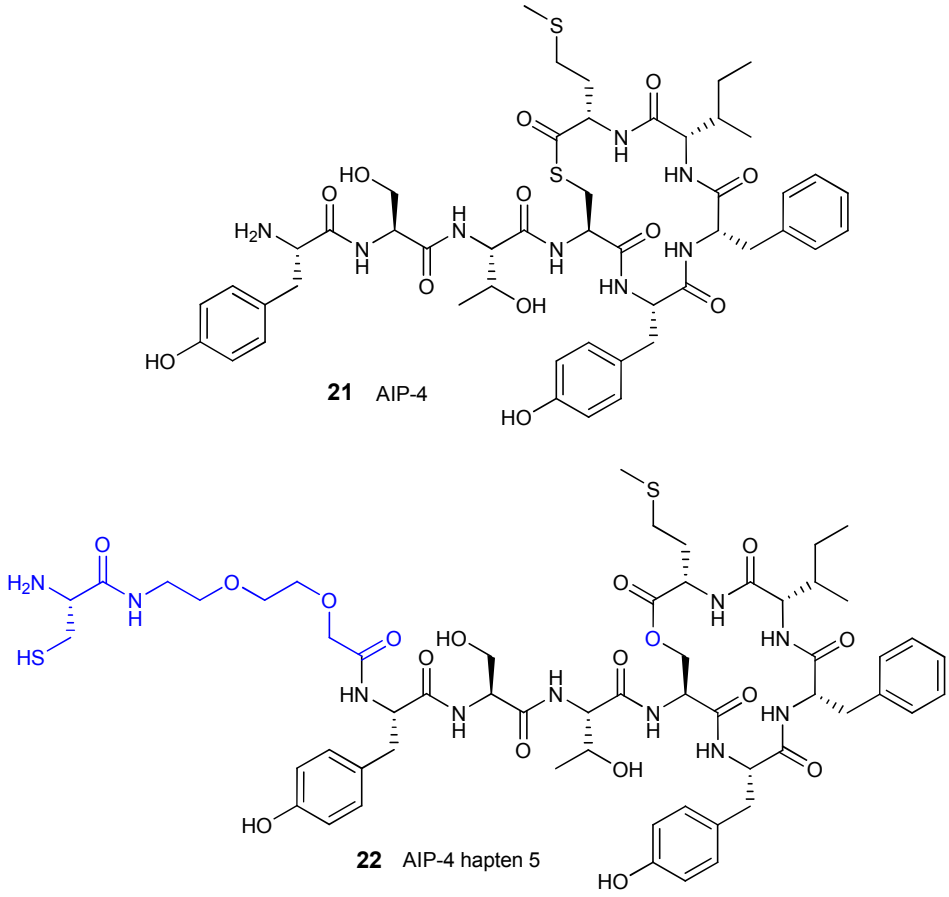


Figure 14. Structures of AIP-4 and AIP-4 hapten-5.

Twenty monoclonal antibodies (mAbs) were prepared and one of them, AP-24H11, had a strong binding affinity for AIP-4 ($K_{d\ AIP-4}$ = 90 nM) when compared to other AIPs ($K_{d\ AIP-1}$ = 5 mM, $K_{d\ AIP-2}$ = 25 mM, $K_{d\ AIP-3}$ = 25 mM). AP-24H11 showed an impressive aptitude to discriminate AIP-1 from AIP-4 (the difference between them one aminoacid, an aspartic acid residue for AIP-1 on position 5 instead of a tyrosine residue for AIP-4). This high level of recognition led the authors to a further investigation of

mAb AP4-24H11 which reduced the expression of α-hemolysin and increased the production of protein A in the strains of group IV, RN4850 and NRS168. Such results are consistent with the hypothesis that mAb AP4-24H11 is able to modulate the quorum sensing in *S. aureus* of group IV. The pathogenicity of *S. aureus* in an *in vivo* abscess formation mouse model could also be suppressed showing that mAbs are feasible tools to suppress QS associated with *S. aureus* virulence.

1.5 AHL Quorum Sensing Pathway

A large number of Gram-positive bacteria uses AHL (acyl homoserine lactone) as signaling molecules in their quorum sensing system. The AHLs consist of a fatty acyl chain that is linked to a lactone (generated from an homoserine) through an amide bond. The AHLs possess a significant chemical diversity among bacteria. Even the same bacteria can synthesize different types of AHLs. The structural divergences are focused on the size and composition of their acyl chain.

Usually the length of the chains has been reported to range between 4 to 16 carbons. The chains may have double bonds which can vary from increments of two carbon units as in C4, C6 and C8. The third carbon in the chain can be a carbonyl or simply bear a hydroxy, or in the simplest case, be fully reduced to an alkyl carbon. The diversity on the third position occurs merely in the biosynthetic process (Figure 15). In the case of *Pseudomonas aeruginosa* for example FabG is responsible for the reduction of the carbonyl of C-3 in acetoacetyl-ACP to d-3-hydroxybutyryl-ACP (Hoang et al., 2002).

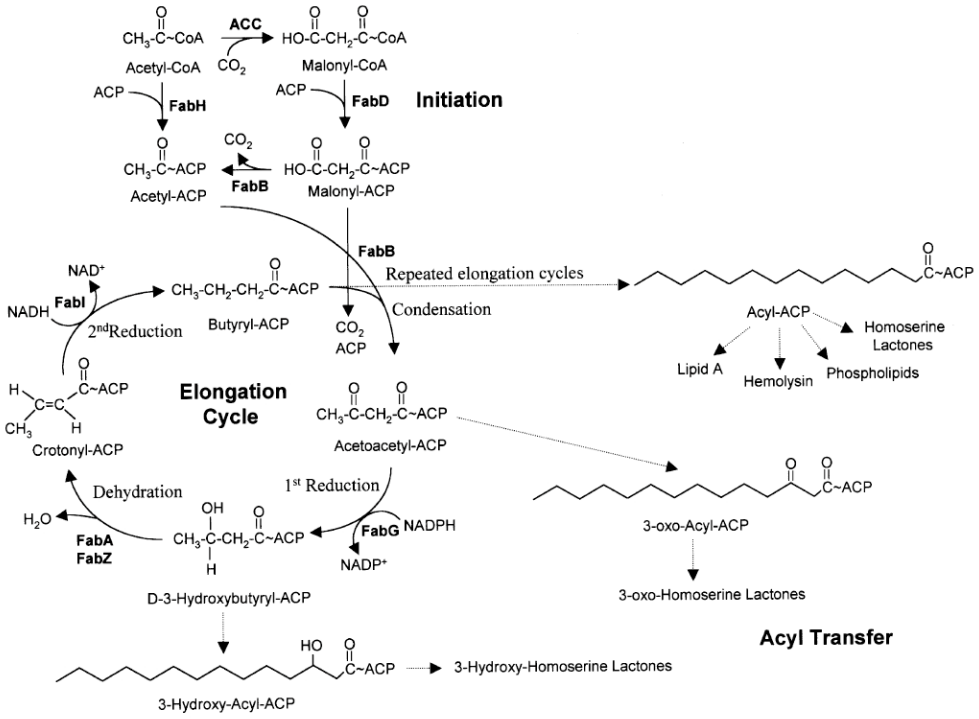
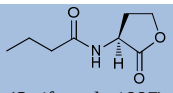
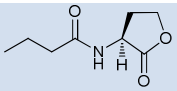
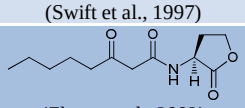
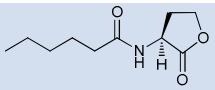
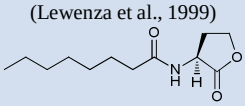
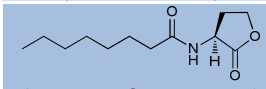
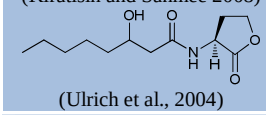
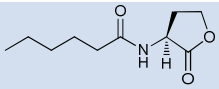
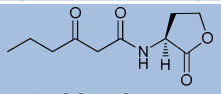
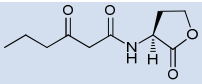
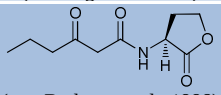
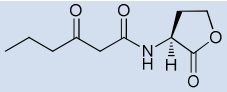
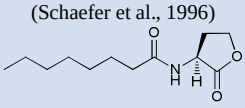
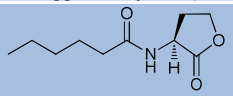
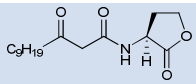
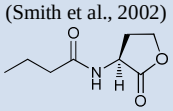
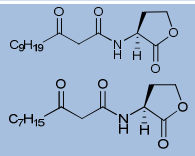
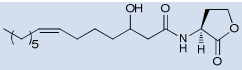
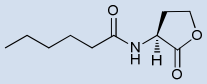
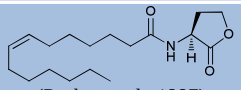
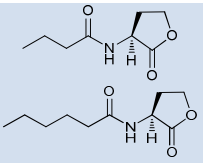
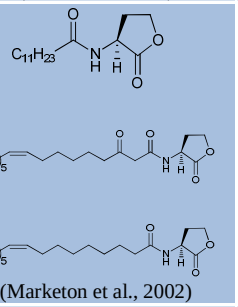
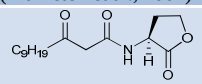
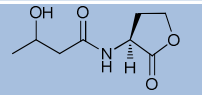
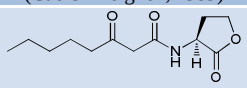


Figure 15. Biosynthesis of homoserine lactones in *Pseudomonas aeruginosa.*

The quorum sensing in Gram-negative is regulated by a large number of regulatory proteins. Among them the Lux-R proteins are the most studied. Most of the Lux-R family of proteins are transcriptional activators responsive to AHL, although the repressors also exist in nature (Swift et al., 1997). Table 2 illustrates the AHL diversity, in addition to the bacteria, signal, regulators, and the expressed phenotype.

Entry	Bacterium	AHL structure	Designation	LuxI/R	QS phenotype	Target or Effect on host
1	*Aeromonas hydrophila*	 (Swift et al., 1997)	BHL, C4	Ahy/AhyR	Exoprotease production	
2	*Aeromonas salmonicida*	 (Swift et al., 1997)	BHL, C4	AsaI/AsaR	Extracellular prorease	
3	*Agrobacterium tumefaciens*	 (Zhang et al., 2002)	OOHL 3-oxo-C8	TraI/TraR	conjugal transfer of the Ti plasmid	Crown gall tumor; large growths on plant host
4	*Burkholderia cenocepacia*	 (Lewenza et al., 1999)  (Sokol et al., 2003)	HHL, C6 OHL, C8	CepI/CepR	Biofilm, swarming motility, virulence	Opportunistic human pathogen; common infection in CF patients; may cause disease in plants
5	*Burkholderia pseudomallei*	 (Kiratisin and Sanmee 2008)  (Ulrich et al., 2004)	OHL, C8 3-hydroxy-C8	PmlI1/PmlR1 PmlI2/BpmR2	Virulence, exoprotease	Melioidosis, affects lungs, heart, brain, liver, kidneys, commonly found in Southeast Asia
6	*Chromobacterium violaceum*	 (McClean et al., 1997)	HHL, C6	CviI/CviR	Exoenzymes, cyanide, pigment	Rare human pathogen, can cause skin lesions and sepsis
7	*Erwinia caratovora*	 (Welch et al., 2000; Burr et al., 2006)	OHHL, 3-oxo-C6	ExpI/ExpR CarI/CarR	Carbapenem, exoenzymes, virulence	Plant pathogen; Common cause of decay in stored fruits and vegetables
8	*Erwinia chrysanthemi*	 (Castang et al., 2006)	OHHL, 3-oxo-C6	ExpI/ExpR	Pectate lyases	
9	*Erwinia stewartii*	 (von Bodman et al., 1998)	OHHL, 3-oxo-C6	EsaI/EsaR	Exopoly-saccharide, virulence factors	
10	*Photobacterium fischeri (Vibrio fischeri)*	 (Schaefer et al., 1996)  (Gilson et al., 1995; Lupp & Ruby 2004)	OHHL, 3-oxo-C6 OHL, C8	LuxI/LuxR AinS/AinR	bioluminescence symbiosis bioluminescence symbiosis	Luminescent bacterium found in light organs of monocentrid fish and sepolid squid
11	*Pseudomonas aureofaciens*	 (Zhang & Pierson 2001)	HHL, C6	PhzI/PhzR	Phenazine antibiotics	

12	*Pseudomonas aeruginosa*	 (Smith et al., 2002)  (Smith & Iglewski, 2003)	OdDHL, 3-oxo-C12 BHL, C4	LasI/LasR QscR RhlI/RhlR	alkaline protease, elastase, cyanide (HCN) production, hemolysin, exotoxin A, neuraminidase, pyocyanin and rhamnolipid production	Oportunistic pathogen; one of the major causes of hospital acquired infections (urinary tract, burn, external ear)
13	*Pseudomonas putida*	 (Steidle et al., 2002)	OdDHL, 3-oxo-C12 ODHL, 3-oxo-C10	PpuI/PpuR	Biofilms	Saprophytic soil bacterium; bioremediation of naphthalene contaminated soils
14	*Rhizobium leguminosarum*	 (Schripsema et al., 1996; Yajima et al., 2008)  (Gray et al., 1996)	3-Hydroxy-7-*cis*-C14 HHL, C6	CinI/CinR RhiI/RhiR RaiI/RaiR TraR BisR	Root nodulation, Symbiosis, plasmid transfer, Growth inhibition	Symbiotic nitrogen fixing bacterium to legumes (e.g. peas)
15	*Rhodobacter sphaeroides*	 (Puskas et al., 1997)	7-*cis*-C14-HSL	CerI/CerR	Dispersal from bacterial aggregates	
16	*Serratia liquefaciens*	 (Eberl et al., 1996)	BHL, C4 HHL, C6	SwrI/SwrR	Extracellular protease, swarming	
17	*Sinorhizobium meliloti*	 (Marketon et al., 2002)	DDHL, C12 3-oxo-9-*cis*-C16 9-*cis*-C16:1	SinI/SinR ExpR TraR	Nodulation and symbiosis	Symbiotic nitrogen fixing bacterium to legumes (e.g. alfafa)
18	*Vibrio anguillarum*	 (Milton et al., 1997)	OdDHL, 3-oxo-C12	VanI/VanR		terminal hemorrhagic septicemia known as vibriosis in fish
19	*Vibrio harveyi*	 (Cao & Meighen, 1989)	3-hydroxy-C_4-HSL	LuxLM/ LuxN	Bioluminescence	
20	*Yersinia pseudo-tuberculosis*		OOHL 3-oxo-C8	YpsR/YpsI	Regulation of clumping and motility	

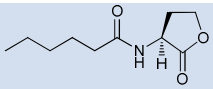
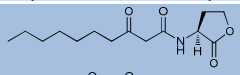
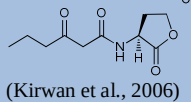
		 (Atkinson et al., 1999)	HHL, C6	YtbR/YtbI		
21	*Yersinia pestis*	  (Kirwan et al., 2006)	ODHL, 3-oxo-C10 OHHL, 3-oxo-C6	YspI/YspR Ype/YpeR	Regulation of clumping and motility	

Table 2. AHLs, bacteria, and receptors associated with their quorum sensing. Phenotype regulated by the QS and effect on the host.

It is interesting to note the immense variety of bacteria that use quorum sensing involving AHLs. The historically relevant species, *Yersinia pestis*, was responsible for a number of epidemic episodes including The Plague of Justinian in 542 A.D. and the Black Death, which occurred from 1347 to 1353 A.D. and wiped out at least one third of the European population. More important is to realize that many of these bacteria produce the exact same chemical signal, but use them for different functions. For example OHHL is produced by *Vibrio fischeri* and by *Yersinia pestis*; two completely different bacteria regarding pathogenicity, yet they are able to provide distinct phenotypic response when in contact with a certain concentration of OHHL.

The LuxR type proteins, which are the receptors of the acyl-HSL, can be subdivided in two domains. The first one contains the binding site which is located near the N-terminal of the protein. Mutations on that site proved to extinguish the binding of 3-oxo-C6-HSL to LuxR (Hanzelka, 1995). Further studies proved that it is also possible to block the effects of cognate autoinducers, generating *per se* an antagonic response (Schaefer et al., 1996). The second domain, containing the C-terminus, has a helix-turn-helix (HTH) motif, which is required for DNA binding. When the binding between the acyl-HSL and the N-terminal domain occurs it leads to a series of conformational

changes that culminate in multimerization of the complex LuxR type protein-acyl-HSL and further DNA binding.

A greater insight of the binding mechanism was acquired with the crystallization of TraR (a close homolog of LuxR from *Agrobacterium tumefaciens*) with its cognate ligand (3-oxo-C8-HSL) and a oligonucleotide, as depicted in Figure 16 (Zhang et al., 2002).

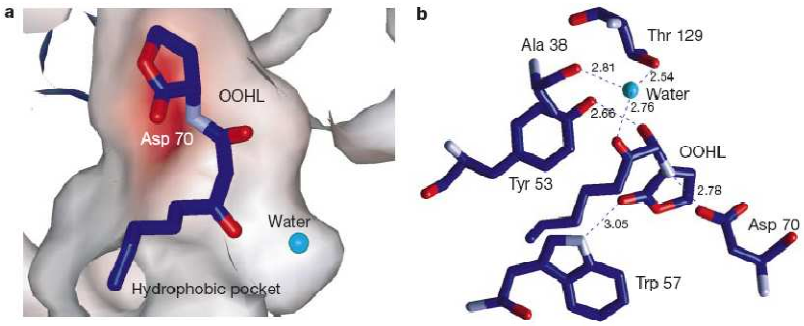


Figure 16. Binding site of 3-oxo-C-HSL after dimerization. (Figure reproduced with permission).

In the case of TrA, after its cognate ligand binds to its site in the N-terminal region, it forms a dimer, with each monomer being composed of two folded domains attached by a flexible linker region. This domain forms an α-β-α sandwich that coordinates ligand interactions through the central β sheet. The central β-sheet has five anti-parallel strands and is curved, with the 3-oxo-C8-HSL bound to its concave surface. The pheromone is fully surrounded by the protein and has no significant contact with solvent. Hydrophobic and aromatic residues comprise most of the 3-oxo-C8-HSL binding pocket. The acyl chain runs parallel to a β-sheet surface and is surrounded by lipophilic side chains in the protein.

The fact that the ligand is completely surrounded by the protein draws a distinction from the typical concept of ligand-receptor in which the receptors hold the ligand-binding site exposed. That indicates that the actual "receptor" for 3-oxo-C-HSL in *Agrobacterium tumefaciens* is the "nascent" unfolded form of TraR (Zhu & Winans, 2001).

After the dimer is formed and the "nascent conformation is changed", the complex binds to DNA through the HTH motif. Transcriptional activation of the associated promoter follows the binding of the *lux* type box.

1.6 Inhibitors of AHL Synthesis

Biofilms, in particular, have received special attention since their formation protects bacteria from treatment with antibiotics as well as from the host immune system. The treatment of bacterial infections where a biofilm is present represents a challenge in therapeutic settings. Concerning this matter, autoinducer analogs were synthesized and tested against *Pseudomonas aeruginosa*. Several proved to be efficient in reducing both virulence factors and biofilm formation (Figure 17) demonstrating that small template molecules based on quorum sensing can provide a new insight to the generation of antibacterial agents (Smith et al., 2003).

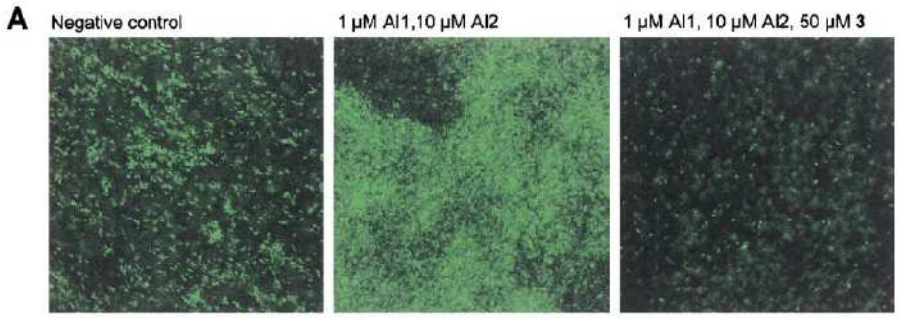
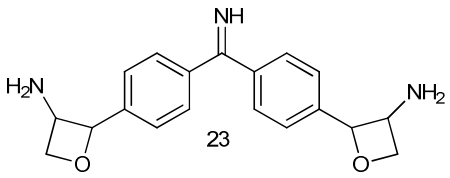


Figure 17. Inhibition of biofilm formation by autoinducers analogs on *Pseudomonas aeruginosa*. (Figure reproduced with permission.

The design and synthesis of artificial AHLs proved to be strong inhibitors of the production of virulence factors, which are necessary for pathogenesis (Geske et al., 2007). This also corroborates the fact that small molecules involved in quorum sensing can serve as templates for the development of new antibacterial agents.

Therefore, the identification of synthetic small molecules that can play either an antagonist or agonist role in the quorum sensing process represents a valid pursuit in the design and development of new antibiotics.

The next section will describe methods for the construction of oxetane rings, based on the recent identification of a new QS molecule, bradyoxetin (**23**; Figure 18).



23

Figure 18. Structure of bradyoxetin.

CHAPTER 2: OXETANE RING SYNTHESIS

2.1 Introduction to oxetanes

Oxetanes are defined as four member ring cyclic ethers. This functional group is present in a number of pharmacologically relevant and complex natural products including the antitumor agent paclitaxel (**24**), the antiviral agent oxetanocin (**25**), and the endogenous antiplatelet agent thromboxane A2 (**26**).

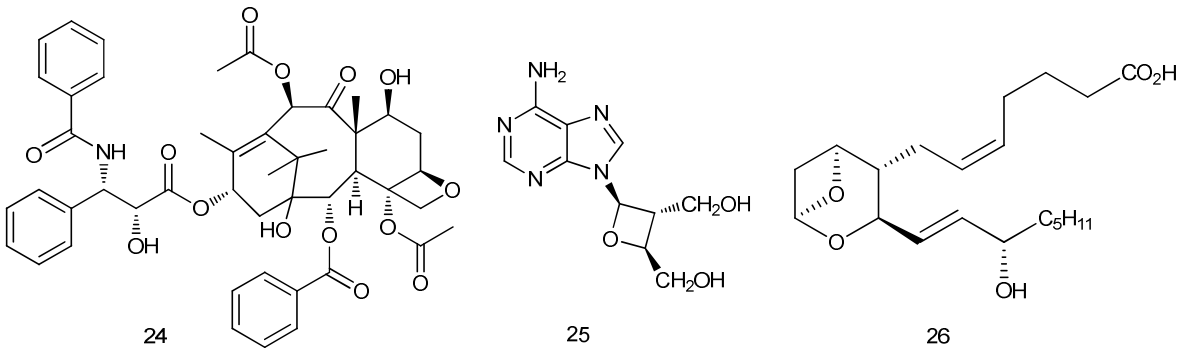


Figure 19. Pharmacologically relevant molecules containing an oxetane ring.

A number of other "less celebrated" natural products containing the oxetane ring have been isolated from nature (Figure 20) including mitrephorone A (**27**; Li et al., 2005), (+)-(Z)-laureatin (**28**; Irie et al., 1968; Irie et al., 1970; Kurosawa et al., 1973), dictyoxetane (**29**), merrilactone (**30**) and one of the simplest oxetanes, oxetin (**31**).

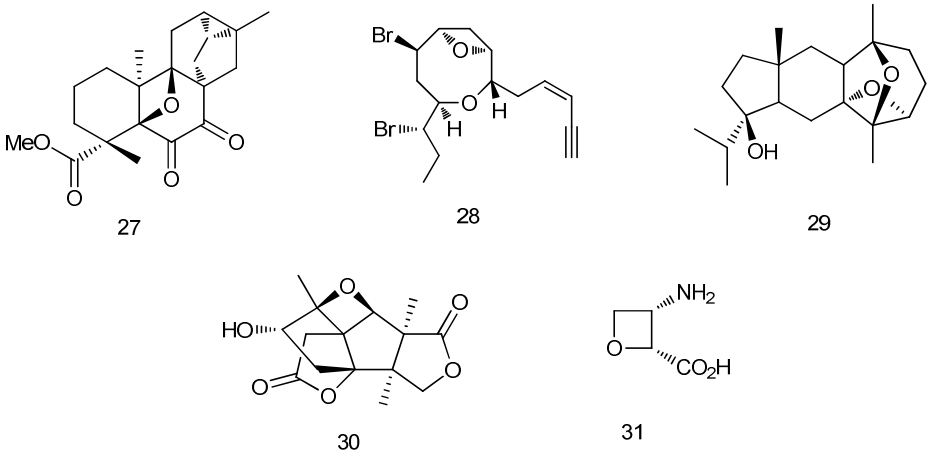
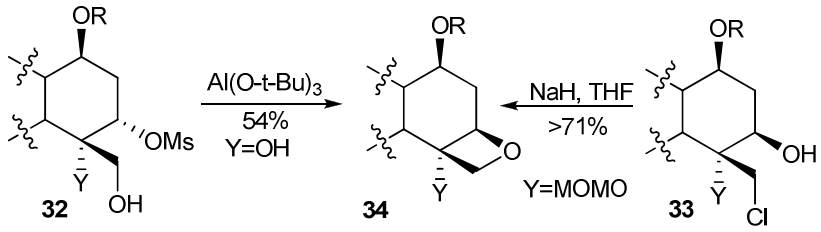


Figure 20. Additional natural products containing an oxetane ring.

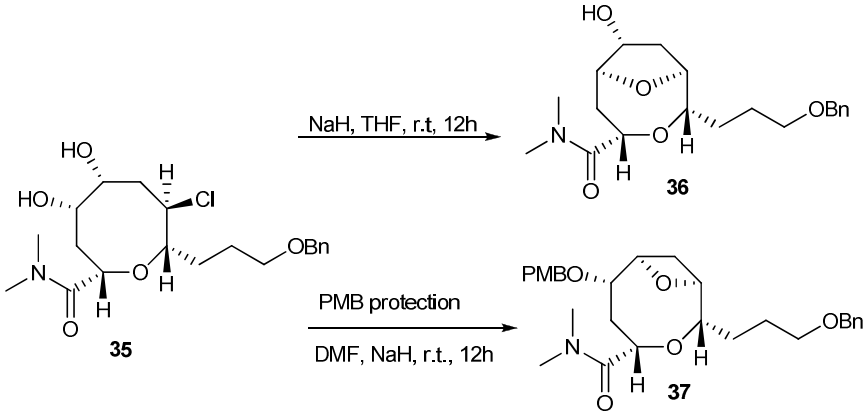
2.1 Synthesis of oxetanes: Intramolecular cyclization reactions

The most common way to synthesize an oxetane ring is through the use of an intramolecular 4-*exo*-*tet*-displacement reaction. This strategy has been used for the incorporation of constrained oxetane rings as in the synthesis of the the natural product paclitaxel and into carbohydrate backbones (Christensen, 2003). Studies have shown that the 4-*exo*-pathway most often is the preferable way to proceed with the cyclization instead of the chemically permitted 5-*exo* and 3-*exo* cyclizations. The leaving groups are commonly mesyl (Brennan et al., 2004), tosyl (Holton et al., 2002; Isaacs et al., 2002) and halogens (Uttaro et al., 2005). Scheme 1 depicts the 4-exo-tet transformation in the synthesis of the oxetane ring of paclitaxel analogs, using precursors **32** or **33** for the construction of **34**.



Scheme 1. Formation of oxetane rings via 4-*exo*-*tet* displacement reactions.

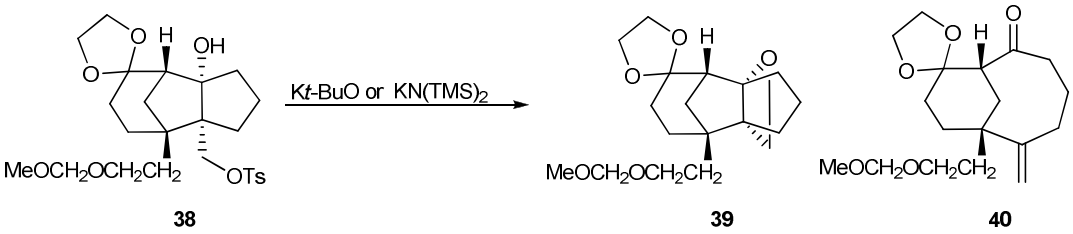
In total synthesis of isomeric laureantins, a 4-*exo*-*tet*-displacement was used to install the oxetane ring (Scheme 2). The beauty with this strategy lied in the formation of a key substrate (**35**) that would serve a double task, namely, for the installment of a furan ring in intermediate (**36**), ultimately used for (+)-3-(Z)-isolaureatin production, and for oxetane ring formation (compound **37**), for (+)-3-(Z)-laureatin synthesis (Kim et al., 2007).



Scheme 2. Synthesis of laureantin and isolaureatin precursors utilizing 4-*exo*-*tet*-displacement reactions.

Oxetane rings were also produced in studies involving the synthesis of gymnomitrane terpenoids (Scheme 3). Treatment of tosylated **38** with bulky non-

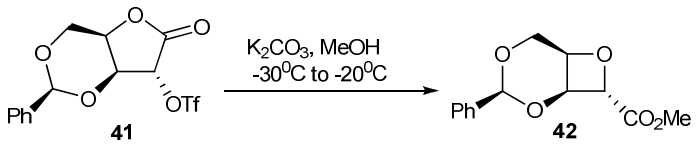
nucleophilic bases led to the formation of oxetane **39** and ring-expanded product **40**, formed as a result of a Grob fragmentation reaction (Toyota et al., 2000).



38 39 40

Scheme 3. Oxetane ring synthesis vs. Grob fragmentation.

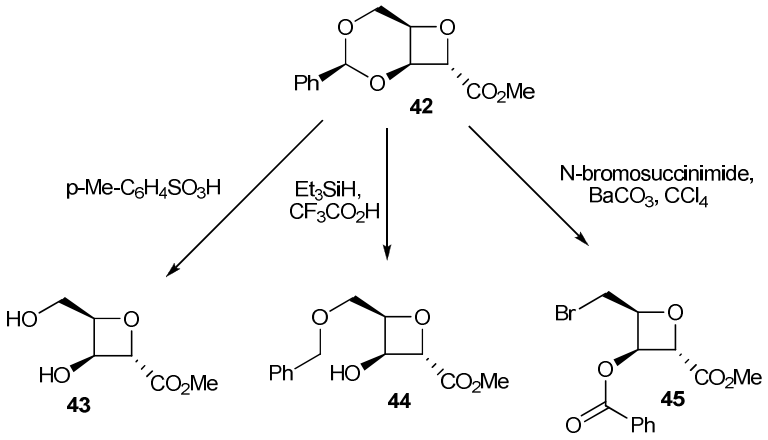
In an attempt to synthesize oxetin (**31**) analogs (Jenkinson et al., 2004), an approach based on the use of chiral pool D-xylose was examined (Scheme 4). The oxetane ring was constructed through a ring contraction of α-triflate-γ-lactone (**41**) with K_2CO_3 in methanol at low temperature, affording bicyclic oxetane **42**.



41 42

Scheme 4. Synthesis of oxetanes through ring contraction of α-triflate-γ-lactones.

The bicyclic oxetane **42** was submitted to three separate reaction types to reveal its utility as a useful building block (Scheme 5). Deprotection of the acetonide afforded diol **43**, while treatment with triethylsilane and trifluoroacetic acid led to the selective formation of secondary alcohol **44** (DeNinno et al., 1995). Finally, a bromination reaction using Hanessian-Hullar conditions with *N*-bromosuccinamide afforded **45** (Hullar & Siskin 2002).



Scheme 5. Generation of oxetane building blocks.

Oxetane **44** was further submitted to a series of protection and S_N2 displacement reactions that ultimately led to the production of azido oxetanes **45** and **46**, suitable latent amine precursors for future drug discovery efforts (Figure 21) (Jenkinson et al., 2004).

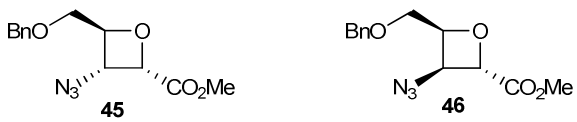
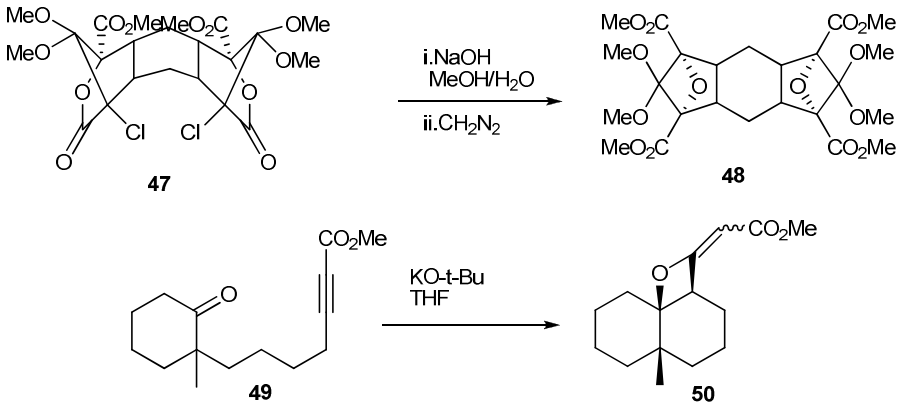


Figure 21. Azido oxetanes as latent amine precursors.

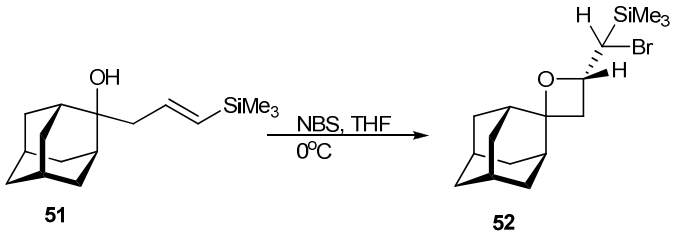
The formation of oxetane **48** from a polycyclic system **47** revealed a very uncommon displacement reaction on a tertiary center (Khan et al., 2005). The conjugate addition of an alkoxide to an alkynoate **49** was also used for the formation of oxetane **50** (Scheme 6) (Wendling & Miesch 2001).



Scheme 6. Uncommon oxetane ring synthesis reactions.

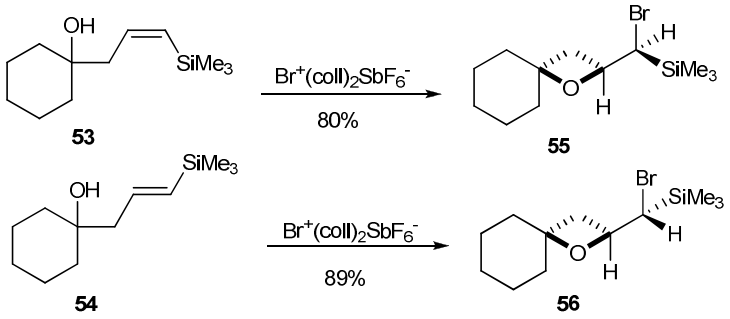
2.2 Synthesis of oxetanes: Electrophilic cyclization reactions

Oxetanes can also be formed through electrophilic cyclization reactions of unsaturated alcohols. One of the first examples reported invoked the addition of NBS to a δ-hydroxy vinylsilane **51** derived from adamantanone (Scheme 6). The product was a curious adamantane spirooxetane **52** (Ehlinger & Magnus 1980).



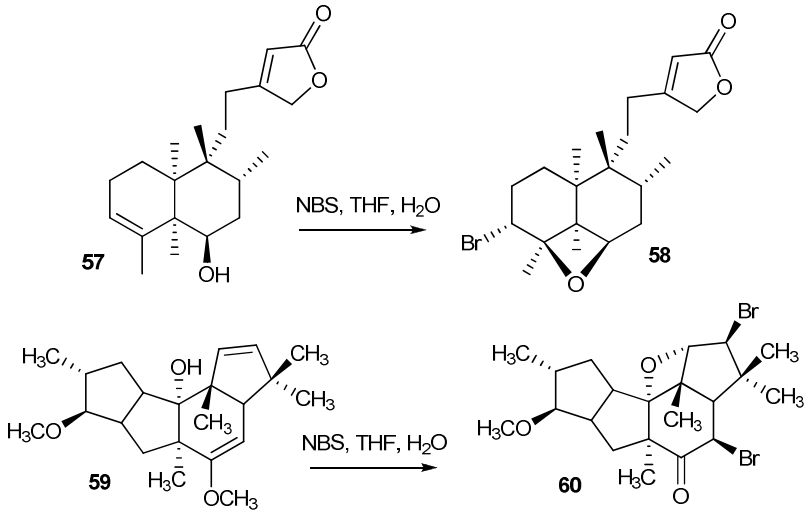
Scheme 7. Synthesis of oxetanes through electrophilic cyclization reactions.

Similar transformations were performed with vinylsilanes to investigate mechanistic issues in the cyclization reaction. For example, vinylsilane homoallylic alcohols **53** and **54** furnished spirooxetanes **55** and **56**, respectively, when treated with bis(*syn*-collidine) bromine(I) hexafluoroantimonite (Rofoo et al., 2001). When the hydroxy group occupied a secondary carbon or, conversely, the proton β to the hydroxy group was substituted with a methyl group, diastereoselectivity was not preserved.



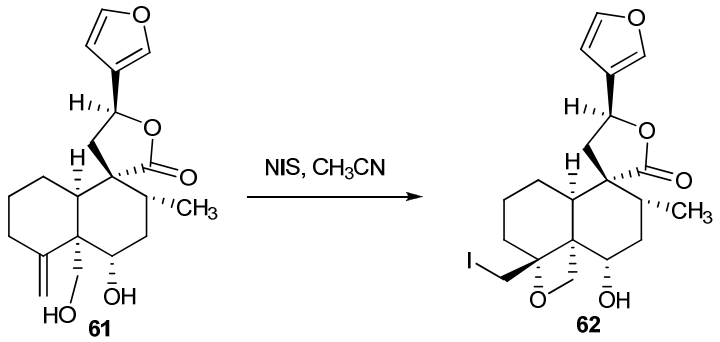
Scheme 8. Synthesis of oxetanes using bis-collidine complexes.

The electrophilic cyclization reaction of homoallylic alcohols using NBS has also provided a powerful method for generating molecules suitable for X-ray crystal diffraction studies and absolute configuration determination (Scheme 8). For example, treatment of **57** with NBS afforded the bromo-oxetane **58** (Manabe et al., 1985), while reaction of **59** with NBS yielded the dibromo-oxetane **60** (Paquette et al. ,1999).



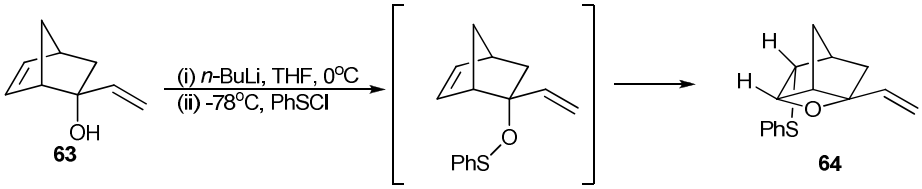
Scheme 9. Reaction of homoallylic alcohols with NBS.

These reaction types are not limited to the use of NBS. In fact, the reactive reagent N-iodosuccinimide (NIS) was also employed in the synthesis of neoclerodane diterpenoids containing an oxetane moiety **62** from its respective homoallylic alcohol **61** (Scheme 9) (de la Torre et al., 2000).



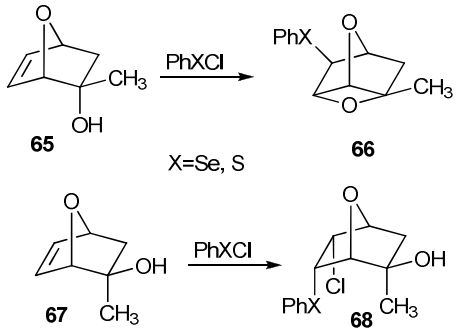
Scheme 10. NIS mediated oxetane synthesis.

Endo-Norborneols containing tertiary hydroxy groups (e.g., **63**) have been reported to react with phenylsulfonyl chloride and *n*-BuLi providing oxetanes (e.g., **64**) and hence generating an intricate oxatricyclo[3.2.1.$0^{3,6}$]octane (Scheme 9) (Brown & Fallis 1985).



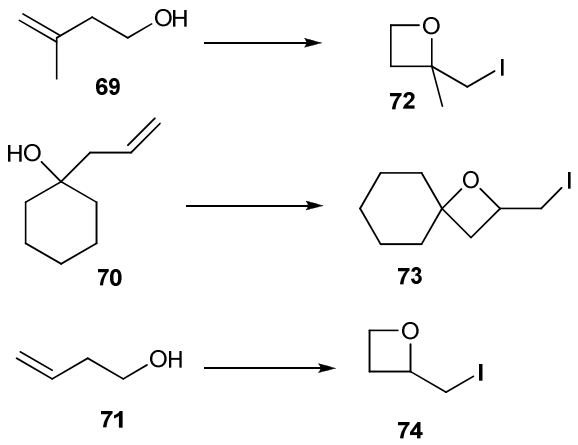
Scheme 11. Synthesis of a tricyclic oxetane from *endo*-Norborneols.

Further studies involving norbornenes were conducted with the aim of investigating the regio- and stereoselectivity of electrophilic addition reactions using phenylselenyl chloride and phenylsulphonyl chloride (Scheme 10). The formation of the oxetane occurred with substrates bearing an *endo*-hydroxy group (**65** to **66**); as anticipated, *exo*-hydroxy substrates **67** failed to produce the oxetane product, but rather, formed the standard olefin addition product **68**. (Arjona et al.,1987; Arjona et al., 1989; Arjona et al., 1992).



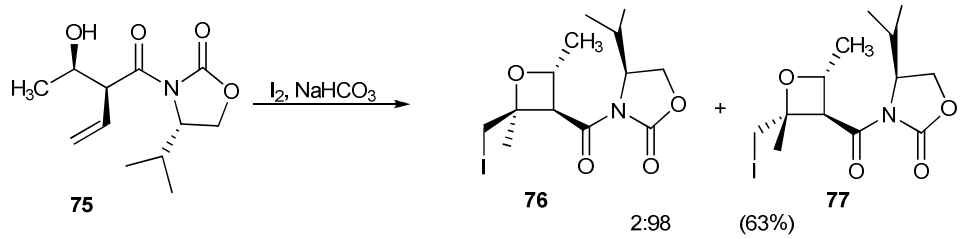
Scheme 12. Stereochemical requirements for oxetane ring synthesis.

Electrophilic cyclization reactions were employed utilizing homoallylic alcohols (**69-71**) and $[I(collidine)_2^+]ClO_4^-$ complexes, generating three to seven member ring iodoethers, including oxetanes (**72-74**), which were produced in satisfactory yields (Scheme 11) (Evans, 1988).



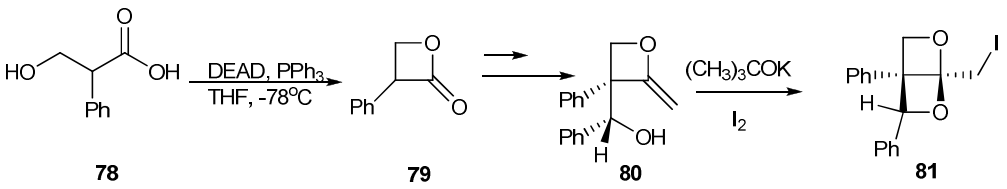
Scheme 13. Synthesis of iodo-oxetanes with $[I(collidine)_2^+]ClO_4^-$.

Electrophile-mediated cyclization reactions of homoallylic alcohols possessing an ester group were also scrutinized. The reaction was prone to form oxetanes in addition to tetrahydrofurans in the presence of iodine and acetonitrile. When silver triflate was added the process suffered a significant acceleration. Generally the cyclizations have presented good stereocontrol for both oxetanes and tetrahydrofurans (Galatsis et al. 1994; Galatsis & Parks 1994; Galatsis et al., 1997). Replacement of the ester with the Evans chiral auxiliary (**75**) afforded oxetane products (**76**-**77**) with a good diastereoselectivity (Scheme 12)



Scheme 14. Evans chiral auxiliary-directed oxetane synthesis.

An interesting report concerning the synthesis of a [2.2.0] fused ketal **81** was disclosed (Wang et al., 1999), prepared from the initial Mitsunobu inversion reaction of **78** in the formation of β-lactone **79** (Scheme 13). This product was carried through several reactions, ultimately leading to the production of compound **80**, subsequently transformed into ketal **81** using an electrophilic cyclization reaction (Dollinger et al., 1999).

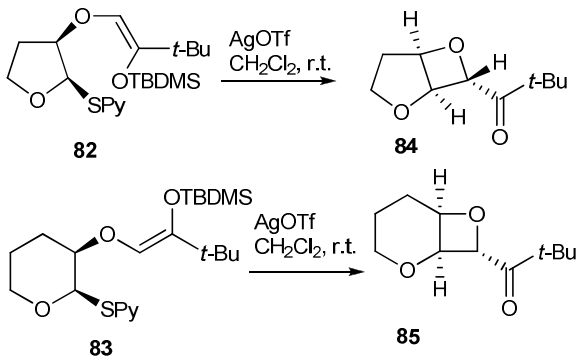


Scheme 15. Synthesis of a [2.2.0] oxetane (ketal).

Other examples involving electrophylic cyclizations for the synthesis of oxetanes include the use of NIS in DCM (Barks et al., 1994), $I(coll)_2ClO_4$ in DCM for the production of oxetane-dimethanols as oxetanocins analogs (Jung & Nichols 1996), and the use of silver(I)oxide (Alonso, 2000) and mercuric triflate (Imagawa, 1998) as electrophilic reagents.

2.3 Synthesis of oxetanes: Cationic cyclization reactions

Cationic cyclization reactions have been used to promote oxetane formation (Craig et al., 1999). Thiopyridyl acetals containing a silyl enol ether (**82-83**) proceed through intramolecular reactions promoted by silver (I) to provide *cis*-[3.2.0] substituted oxetanes (**84-85**) bearing an *exo*-acyl group (Scheme 14).



82 84

83 85

Scheme 16. Cationic cyclization reactions of thiopyridyl acetals.

The cyclization reactions were conducted with pure diastereomer substrates in order to gain mechanistic insight. A model to explain the cyclizations was proposed in which the oxetane ketone substituent is placed *exo*- on the bicyclic system. The silyl enol ether was not reactive using these cyclization conditions. The reaction proved to be consistent with the existence of an intermediate carbenium ion (Figure 22).

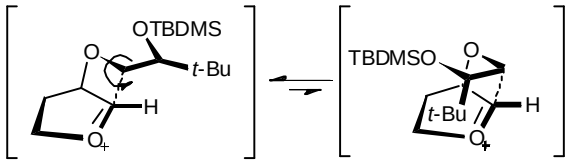
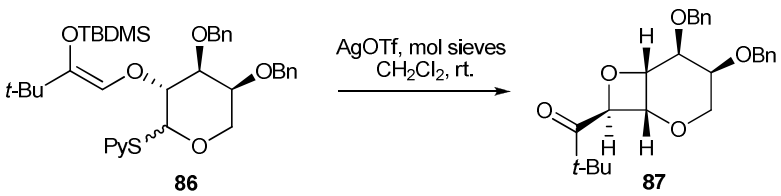


Figure 22. Cationic intermediates in cyclization reactions.

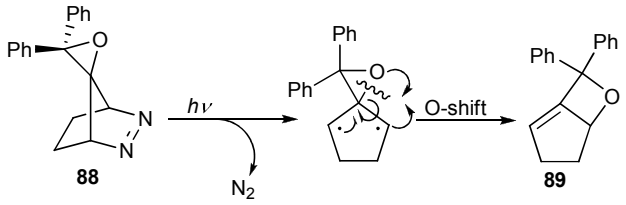
Similar reaction conditions were employed using carbohydrate substrates, since more highly oxygenated systems could have impaired the stability/lifetime of the anomeric cations (Scheme 15). The same authors provided a similar example where the generated cation is stabilized by an exocyclic thioether.



Scheme 17. Carbohydrate substrates in cationic cyclization reactions.

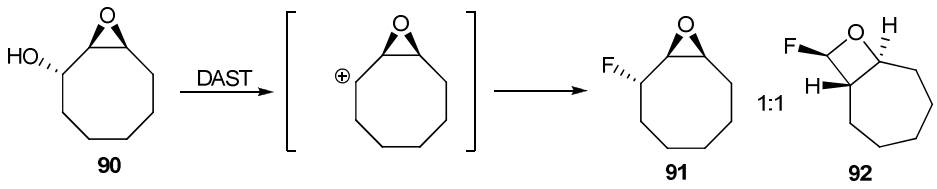
2.4 Synthesis of oxetanes: Rearrangment of epoxides

Azo-epoxides **88** can undergo photochemical fragmentation to provide oxetanes (e.g. **89**) through a 1,2-shift of the C-O bond in the intermediate diradical (Scheme 16) (Abe et al., 2002).



Scheme 18. Photofragmentation of azo-epoxides to produce oxetanes.

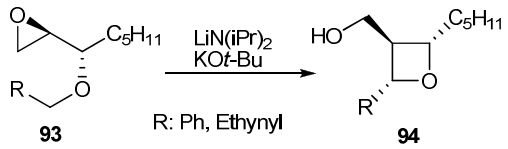
trans-2,3-Epoxycyclooctanol (**90**) reaction with DAST provided the expected epoxy fluoride **91** as well as a 2-fluorooxetane (**92**) (Scheme 17). The explanation for the formation of **92** is based on the classic Wagner-Meerwein shift (Lakshmipathi et al., 2002).



Scheme 19. Synthesis of oxetanes through epoxide rearrangements.

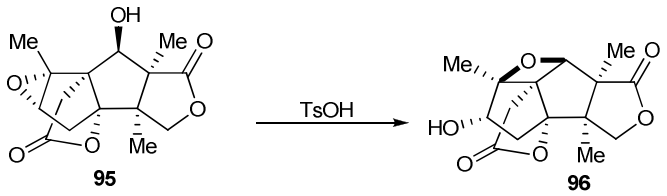
Chiral hydroxyoxetanes (**94**) are produced as a result of an intramolecular 4-*exo*-cyclization reaction when benzyl or propargyl ether tethered epoxides (**93**) and mixed

alkyllithium and/or metal alkoxide superbases like LIDAKOR are used (Scheme 18) (Mordini et al., 2001).



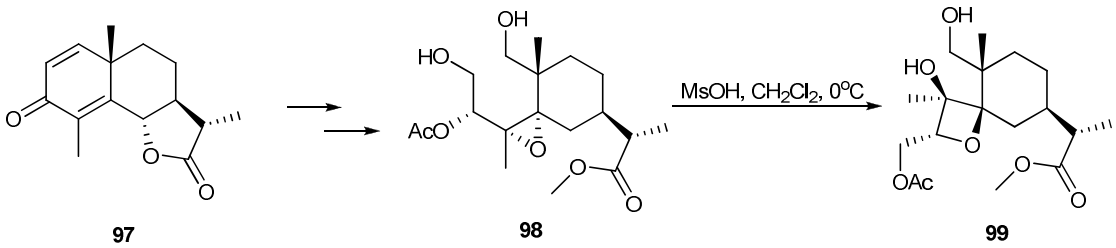
Scheme 20. Synthesis of oxetanes via cyclization reactions of epoxy ethers.

3,4-Epoxyalcohols can suffer isomerization under acidic or basic conditions, as observed in the synthesis of dictyoxetane (Proemmel et al. 2002), first isolated from the known brown algae *Dictyota dichotoma* (Pullaiah et al., 1985) (Rao et al., 1986). The same observations were exploited in the final step of merrilactone synthesis (Birman & Danishefsky 2002; Inoue et al., 2006; He et al., 2007; Inoue et al., 2007). The literature refers to this rearrangement as an acid-induced homo-Payne rearrangement (Scheme 19). A similar acid-promoted tandem rearrangement-cyclization reaction was observed in epoxyalcohols containing benzyl ethers (Mosimann, 2000).



Scheme 21. Homo-Payne rearrangement in the synthesis of merrilactone.

During the synthesis of phytuberin, it was found that diol **98** [generated from the starting material (-)-α-santonin (**97**)] treated with methanesulfonic acid, proceeded through an uncommon 4-*endo-tet* cyclization, generating an unexpected oxetane **99** (Scheme 20) (Prange et al., 2003).

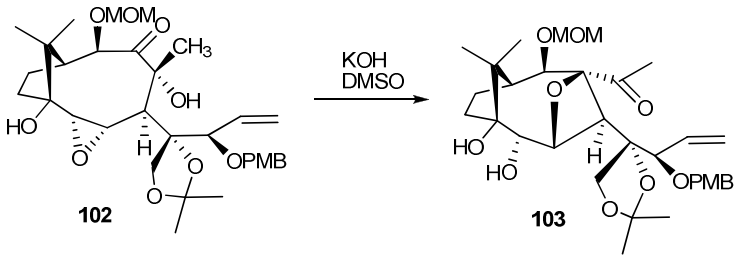


Scheme 22. Formation of oxetanes through 4-*endo-tet*-cyclization.

In the first total synthesis of laureatin (Sugimoto et al., 2007), the authors exploited a biogenetic pathway in an attempt to convert an oxocene to bicyclic skeletons by using a bromo-cationic cyclization reaction. Unfortunately, undesirable cyclization reactions forced the group to seek an alternative route that would provide the laureatin skeleton. The successful pathway exploited a 4-exo-tet cyclization reaction of the epoxyalcohol **100** with KOH in DMSO at 80°C affording oxetane **101** (Scheme 21).

Scheme 23. Synthesis of laureatin precursors via epoxyalcohol rearrangements.

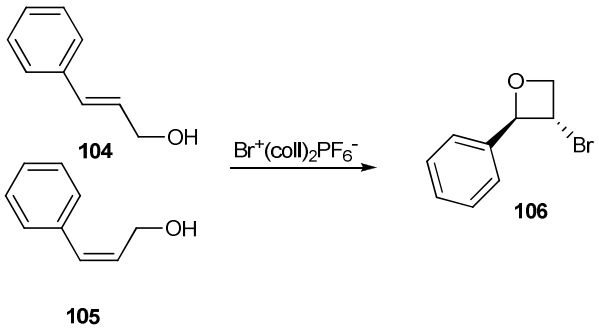
An unusual oxetane ring formation reaction was reported in attempts to prepare paclitaxel using model substrates; a transannular cyclization and rearrangement occurred when epoxide **102** (Scheme 22) was treated with KOH in DMSO, leading to the formation of oxetane **103** (Johnston et al. 1998).



Scheme 24.Oxetane synthesis through an α-ketol ring contraction.

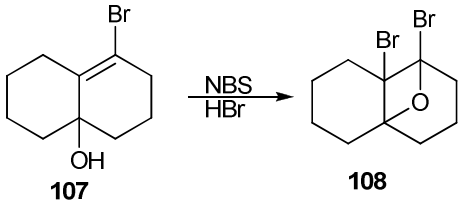
2.5 Synthesis of oxetanes: 4-endo cyclization reactions

The formation of oxetanes through 4-*endo*-cyclizations is uncommon. The examples reported in the literature utilize allylic alcohols as substrates and bis(collidine)bromine(I) hexafluorophosphate (Homsi & Rousseau 1998). Cinnamic alcohols **104** or **105** produce the same *trans*-substituted oxetane **106**, implying cationic intermediates (Scheme 23).



Scheme 25. Example of a 4-*endo* cyclization reaction.

Studies on reaction of bicyclo[4.4.0] bridgehead alcohols **107** with NBS also suggests a 4-endo cyclization reaction, with the formation of dibromo-oxetane **108** (Scheme 24) (Wempe & Grunwell 1995).



Scheme 26. Synthesis of a dibromo-oxetane.

.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

Our initial efforts are directed towards the total synthesis of the unique quorum sensing molecule bradyoxetin (**23**), in an attempt to confirm its absolute configuration and to explore opportunities for analog synthesis (Figure 23). A total synthesis of the four possible stereoisomers and comparison with the data from the natural product would confirm its structure. To date, there are no reported syntheses of bradyoxetin.

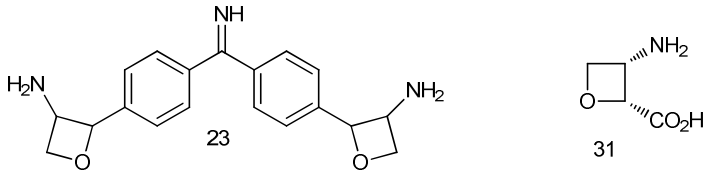
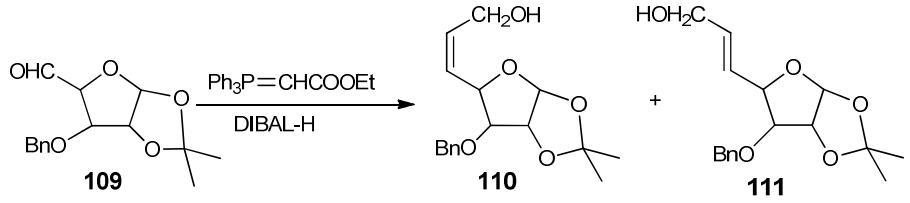


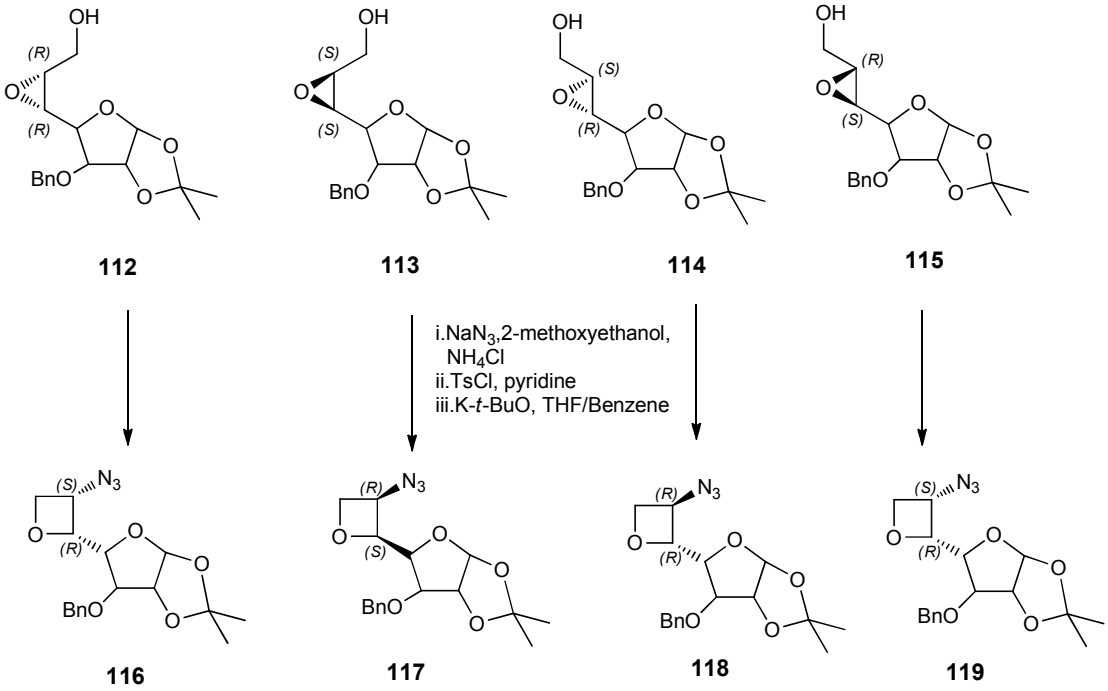
Figure 23. Bradyoxetin and oxetin structures.

Our first approaches towards the synthesis of bradyoxetin were based on the first total synthesis of (2*R*,3*S*)-3-aminooxetane-2-carboxylic acid (**31**, oxetin), an amino acid oxetane isolated from *Streptomyces* sp. OM-2317 (Omura et al., 1984). Its absolute configuration was determined by X-ray crystallography and later confirmed by total synthesis (Kawahata et al., 1986). The first reported and rather cumbersome synthesis of **31** began with aldehyde **109**, synthesized in several steps from D-glucose (Scheme 25). Reaction of **109** with the appropriate phosphorane using standard HWE conditions afforded a mixture isomeric esters, separable by silica gel chromatography. The reduction of the esters with DIBAL-H furnished *Z*- and *E*-allylic alcohols (**110** and **111** respectively) as shown in Scheme 25.



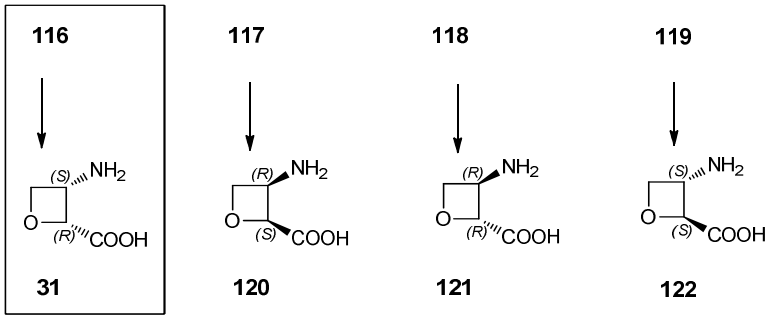
Scheme 27. Initial steps of the D-glucose pathway for oxetin synthesis.

Independent reactions of **110** and **111** with *m*-CPBA afforded a mixture of four diastereomeric epoxides (**112-115**). The epoxides were separated using standard chromatographic techniques, and subsequently were converted to azido-oxetanes (**116-119**) in three steps following a procedure previously reported (Scheme 26) (Behrens, 1983).



Scheme 28. Azido-oxetanes derived from chiral epoxides.

Each azido-oxetane (**116-119**) was converted to an oxetin isomer through a six-step sequence that involved: i.) hydrogenation (10% Pd/C) to convert the azide to the amine group; ii.) protection of the amine with a CBz group; iii.) deprotection of the acetonide auxillary with 0.1 N H_2SO_4 to furnish 1,2 deprotected furanosides; iv.) reduction with sodium borohydride; v.) oxidation with sodium periodate and $RuCl_3$; vi.) CBz group deprotection. This yielded four pure stereoisomers, of which, the oxetane product derived from **116** matched with the naturally occurring product, and its structure was confirmed as (2*R*,3*S*)-3-aminooxetane-2-carboxylic acid (**31**) (Scheme 27).

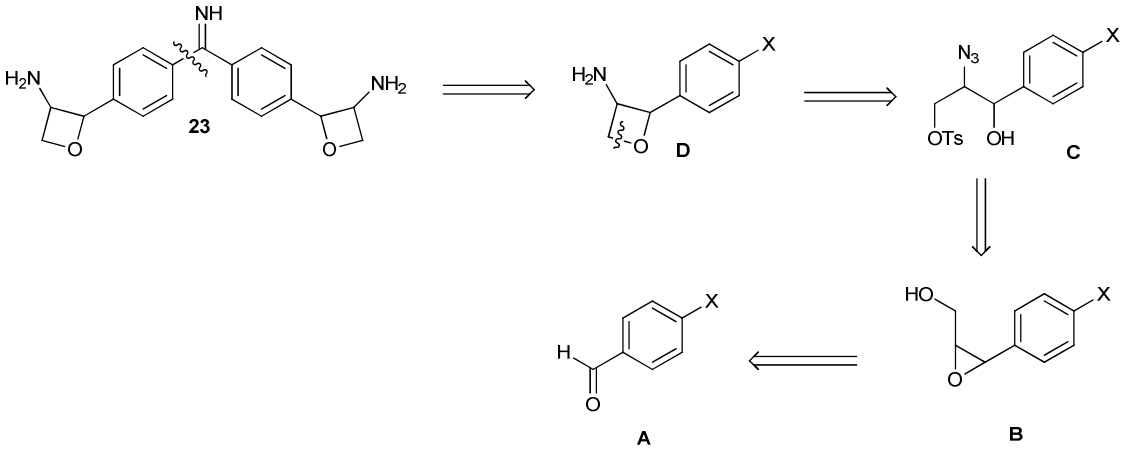


Scheme 29. Synthesis of oxetin and its stereoisomers.

3.2 First Synthetic Approach to Bradyoxetin

Based on the synthesis reported for oxetin, a retrosynthetic approach was formulated (Scheme 28) where the key features invoked the use of an appropriate aldehyde **A** in either a Wittig reaction for the generation of *E*-cinnamic esters, or conversely, a Horner-Wadsworth-Emmons (HWE) reaction for the generation of the *Z*-cinnamic esters. Standard DIBAL-H reduction of the α,β-unsaturated esters followed by a Sharpless epoxidation reaction of the resulting allylic alcohols would lead to chiral

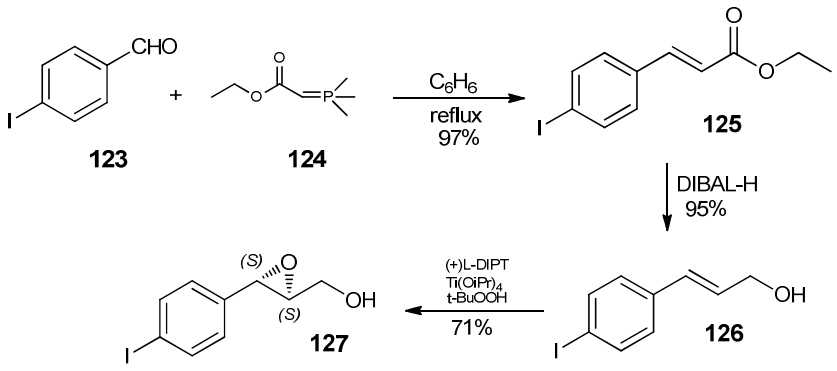
epoxides (**B**). The epoxide stereoisomers would then be converted in independent reactions to the mono-tosylated amine (**C**) for the creation of oxetanes (**D**). To produce the symmetrical imine we envisioned using cobalt octacarbonyl catalysts to generate a ketone (Enquist et al., 2003) subsequent conversion to the hydroxylamine (Ulbrich et al., 2006) and finally, to the requisite product **23** (Akazome et al., 1990).



Scheme 30. First retrosynthetic approach to bradyoxetin.

Our first synthetic approach began with a simple Wittig reaction between 4-iodobenzaldehyde (**123**) and (carbethoxymethylene)triphenylphosphorane (**124**) which yielded the E-ester **125** as the predominant product (Scheme 29) (Couladouros & Soufli 1995). The ester obtained from this reaction contained a minor amount of the *Z*-isomer which was not separated at this stage. Ester **125** was reduced to the allylic alcohol **126** with DIBAL-H (Boger et al., 1994). This product was submitted to a Sharpless asymmetric epoxidation yielding ((2*S*,3*S*)-3-(4-iodophenyl)oxiran-2-yl)methanol (**127**)

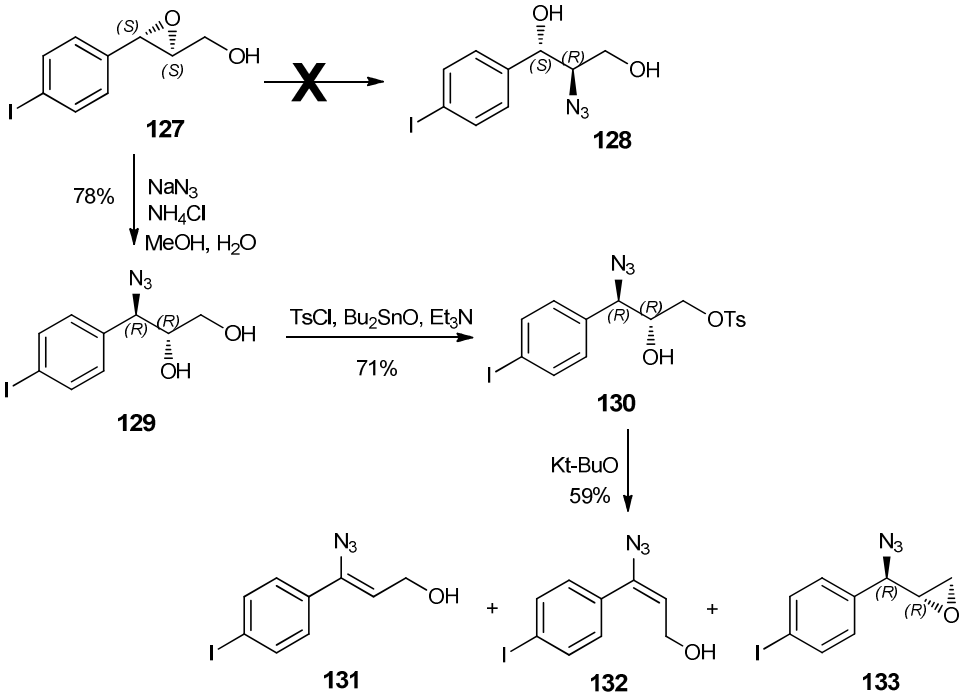
using titanium isopropoxide, (+) L-diisopropyltartrate and *t*-butylhydroperoxide (Boger et al., 1994).



Scheme 31. Synthesis of chiral epoxide 127 from 4-iodobenzaldehyde.

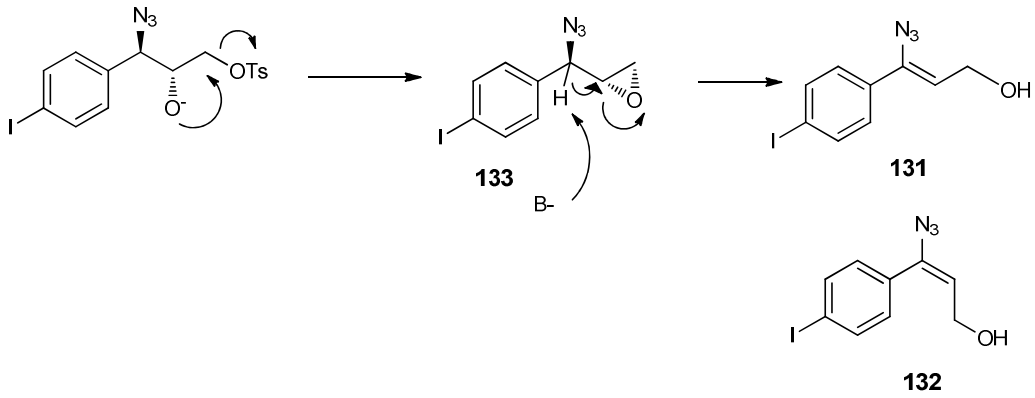
The Katsuki-Sharpless asymmetric epoxidation (Katsuki & Sharpless 1980) opened a new spectrum of possibilities in the context of chiral synthesis of compounds with relevant biological activity. It has been extensively applied to reactions of 2,3-epoxyalcohols with a variety of nucleophiles (Hanson, 1991). It is noteworthy that the synthetic utility of these intermediates is highly dependent on the regioselectivity of the addition reaction. The majority of epoxides are reactive towards metal azides or even organoazides, such as Me_3SiN_3. In order to improve their reactivity, the addition of catalysts to the reaction are usually employed. Common catalysts include ammonium salts (Bonini et al., 1995; Schneider, 2000), $AlCl_3$ (Fringuelli et al., 2001) and copper(II) salts (Fringuelli et al., 2003). The regioselectivity of azidolysis is very similar to that of other nucleophiles. To summarize, monoalkyl epoxides suffer nucleophilic attack by azides preferentially at the terminal methylene group where styrene-based epoxides suffer attack on the benzylic carbon.

The epoxide **127** was subsequently reacted with sodium azide in methanol in order to generate the required 1,3-diol **128** (Scheme 30). Unfortunately, analysis of the azide addition product by ^{1}H-NMR and ^{13}C-NMR techniques was ambiguous to assign of the location of the azide group. A very simple and efficient way to differentiate 1,2-diols from 1,3-diols lies not on spectroscopic methods, but on organic chemistry. 1,2-diols, when treated with HIO_4 produce aldehydes which would be very easy to detect. On the contrary 1,3-diols do not cleave when reacted with HIO_4 (Smith, 2007). Treatment of the azide addition product with HIO_4 led to the formation of an aldehyde product (IR analysis), which suggested that the azide addition product corresponded to structure **129**.



Scheme 32. Reaction of epoxide 127 with sodium azide and subsequent reactions.

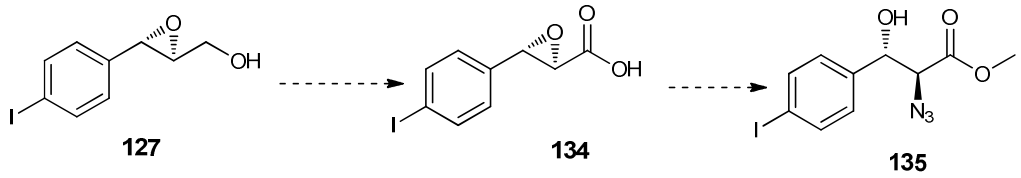
Further confirmation of the azide addition product was realized when azido-1,2-diol **129** was then reacted with tosyl chloride, dibutyltin oxide and triethylamine in anhydrous DCM to afford mono-tosylated derivative **130** (Martinelli et al., 1999), confirmed by analysis of the ^{1}H- and ^{13}C-NMR spectra. Azido tosylate **130** was submitted to basic conditions (potassium tert-butoxide) to provide a mixture of three compounds, **131-133**. Compound **133** proved to be an epoxide due to its distinct shifts in the ^{1}H- and ^{13}C-NMR spectra. The spectroscopic data obtained for compounds **131** and **132** were diagnostic for isomeric olefins, which led us to the conclusion that epoxide **133** generated was subject to additional chemical reactions, namely, elimination reactions (Scheme 33).



Scheme 33. Proposed mechanism for the formation of elimination products.

Overall, the picture was clear: nucleophilic attack of azide on epoxide **127** leads to the production of azido-diol **129**, being governed by the inductive effect of the aromatic ring. In order to produce the correct azide regioisomer, we chose to install a carbonyl pendant to the epoxide ring. The generation of epoxy carboxylic acid **134**

(Scheme 32), would shift the postition of the nucleophilic attack and provide the desired regioisomer **135** (Boger et al., 1994).

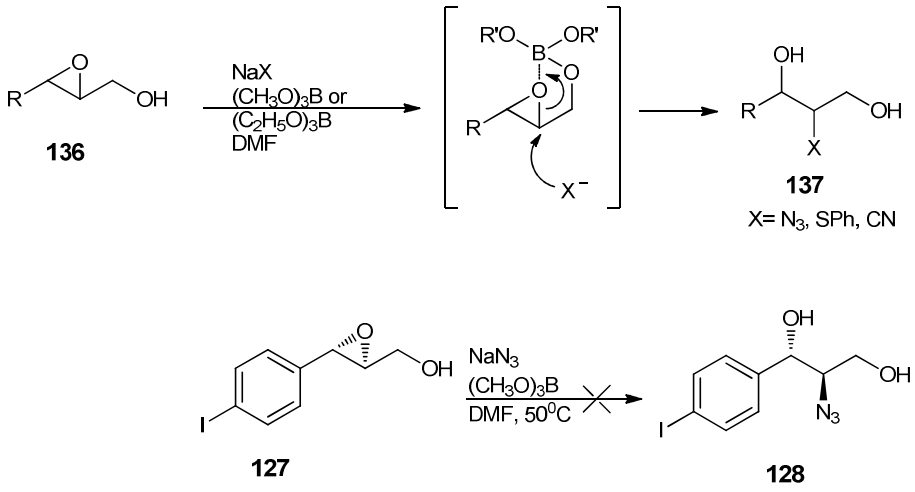


Scheme 34. Proposed installment of a carbonyl group.

In order to capitalize on using carboxylic acid epoxides (e.g., **134**) epoxide **127** required an oxidation. Three oxidation reactions were attempted and included the use of ruthenium chloride and sodium periodate (Denis, et al. 1986), pyridinium dichromate in DMF (Boger, et al. 1994) and periodic acid and chromium oxide (Zhao, et al. 1998). None of the synthetic methodologies provided the desired carboxylic acid epoxide **134**. It is noteworthy that Boger applied similar chemical strategy in the total synthesis of bouvardin, *O*-methyl bouvardin and *O*-methyl-N^9-desmethylbouvardin. In his reported syntheses, three distinct methods for the generation of 1,3-diols bearing a 4-iodophenyl moiety were also examined: treatment of an epoxy ester with aqueous methylamine, reaction of the epoxyalcohol with isocyanate and further hydrolysis of carbamates with introduction of an azide using a Sharpless asymmetric dihydroxylation (Boger & Yohannes 1991). Boger's approach using a Sharpless dihydroxylation was considered, but not applied due to the high price of the chiral auxiliary used in the reaction.

An alternative solution to the problem surfaced, with the realization that chelating agents such as trimethylborate can be used to direct nucleophilc attack (Sasaki et al., 2003). The chelation effect is evident when comparing reactions that use ammonium

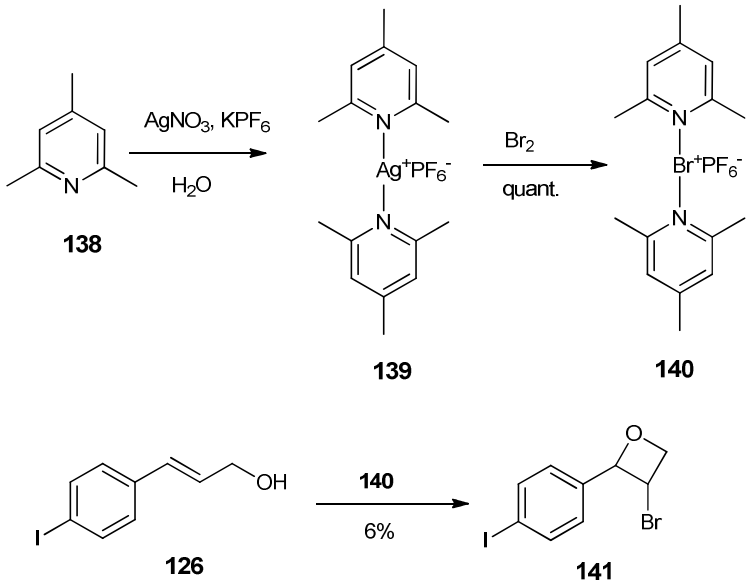
chloride as a catalyst. In the trimethylborate-directed reaction (Scheme 33), complexation of the borate to the pendant hydroxy group of epoxy alcohol **136** polarizes the non-substituted carbon and makes it more reactive as an electrophile, leading to azido-1,3-diol products **137**. When this reaction was performed on **127**, the anticipated azido-1,3-diol **128** was not formed, but rather, the azido 1,2-diol **129**. It appears that coordination between boron and oxygen was not suitable to overcome the effect provided by the presence of the aromatic ring which prompted us to seek an alternative strategy.



Scheme 35. Use of chelation control in epoxide ring opening reactions.

3.3. Second Synthetic Approach to Bradyoxetin

Our second approach relied on the direct synthesis of oxteanes from allylic alcohols (Scheme 34). Several precedents guided this approach: the reactions of allylic alcohols with halogenated collidine complexes to generate oxetanes (Homsi & Rousseau 1999) and the possibility of conducting S_N2 reactions on oxetanes with the retention of configuration (Jenkinson et al., 2004; Johnson et al., 2004).



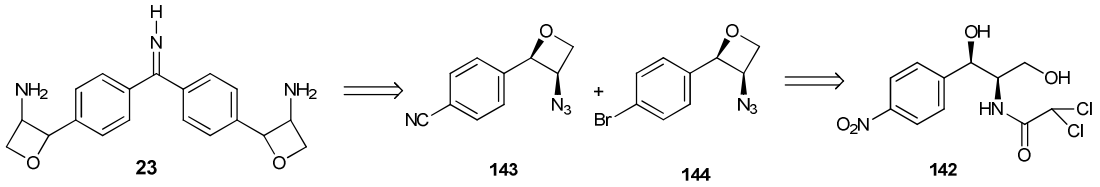
Scheme 36. Collidine complexes for the synthesis of oxetanes.

Bis(collidine)bromine(I) hexafluorophosphate (**140**) was formed from the reaction between bromine and bis(collidine)silver(I) hexafluorophosphate (**139**) (Clausen & Bols 2000). The silver(I) complex **139** was generated from the reaction of collidine (**138**), silver nitrate and potassium hexafluorophosphate in water (Homsi et al., 2000). The reaction of **140** and allylic alcohol **126** afforded a low-yielding mixture of bromo-

oxetanes **141**. Although the yields were dismal, this reaction represented the first successful synthesis of oxetanes whose structures were confirmed by ^{1}H NMR and ^{13}C NMR. Preliminary studies invoking substitution reactions with azide and **141** failed to yield substitution products. The drawbacks of this approach were the low yield of oxetane products, the failure of replacing the halogen with an azide group through S_N2 reaction, and the lack of asymmetric control in the synthesis. This approach was abandoned in favor of a more robust synthesis.

3.4. Third Synthetic Approach towards Bradyoxetin

The third approach takes advantage of the stereochemical features inherent in the natural product chloramphenicol (**142**) a broad spectrum antibiotic that was first isolated from *Streptomyces venezuelae* in 1947 (Scheme 35) (Ehrlich et al., 1947). We envisioned that **142** could be transformed into differentially substituted oxetanes **143** and **144**, suitable for a metal-mediated coupling *en route* to the synthesis of bradyoxetin (**23**).

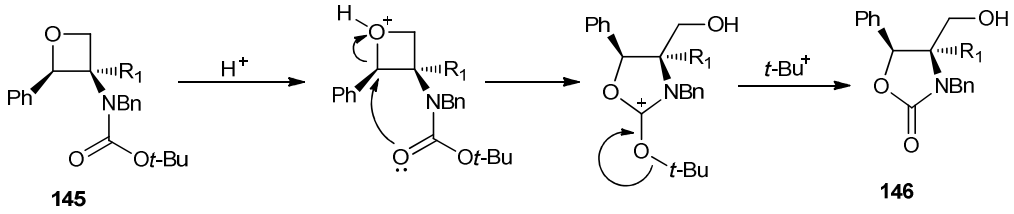


Scheme 37. Chloramphenicol approach for bradyoxetin synthesis.

The advantages of using chloramphenicol as a starting material are twofold: 1.) it is inexpensive and commercially available, and 2.) it is a chiral starting material whose regiochemical configuration is already defined for the formation of aminooxetanes.

Furthermore, both enantiomers of choramphenicol and its amide hydrolysis product are commercially available.

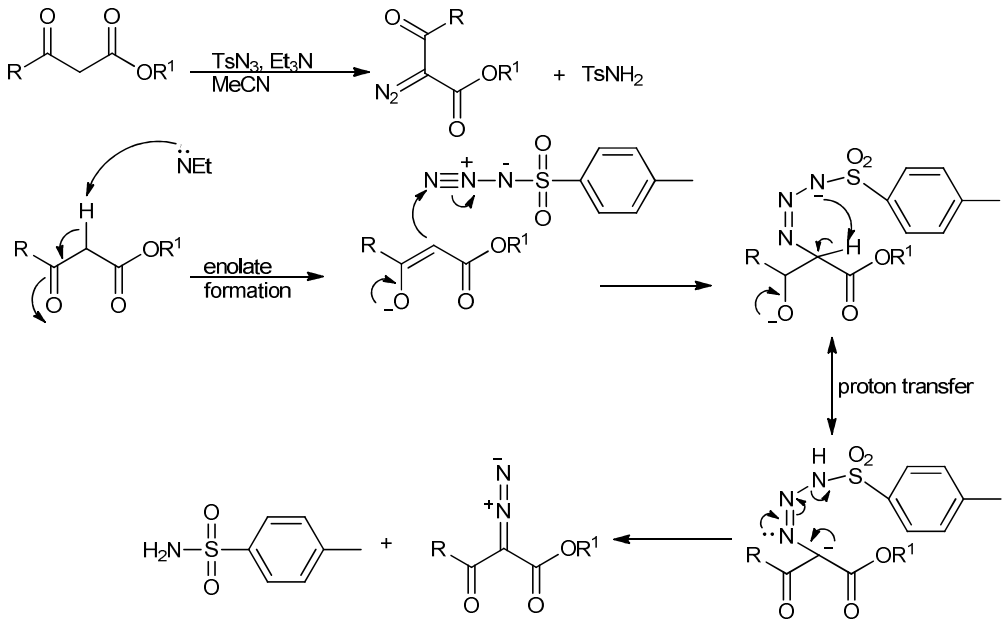
The main challenge at hand was to choose a reasonable protecting group strategy. The azide group was selected, insofar as it would serve as a latent protecting group for an amine during the construction of amino-oxetanes. Carbamate protecting groups pendant to an oxetane ring (e.g., **145**), suffer a rearrangement during its attempted removal with trifluoroacetic acid, leading to oxazolidines **146** (Scheme 36) (Bach & Schröder 1997; Bach & Schroder 1999). Azides possess multiple advantages over other amine protecting groups, the most obvious residing its chemical stability to a wide variety of reaction conditions (Nyffeler et al., 2002).



Scheme 38. Rearrangments of N-Boc oxetanes in the presence of TFA.

In order to employ an azide as a protecting group, the amine functionality in chloramphenicol had to be transformed to the azide. A robust method for this transformation is the diazotransfer reaction (Nyffeler et al., 2002). There are two types of diazotransfer reactions described in the literature. The most common is referred to as a Regitz diazotransfer reaction (Regitz, 1967) which involves the transfer of a diazo group

from a tosyl- or mesyl-azide to an active methylene group. The methylene group can be a part of a 1,3-diketone and the reaction demands the use of a base such as Et_3N in order to proceed with the formation of an enolate (Scheme 37).

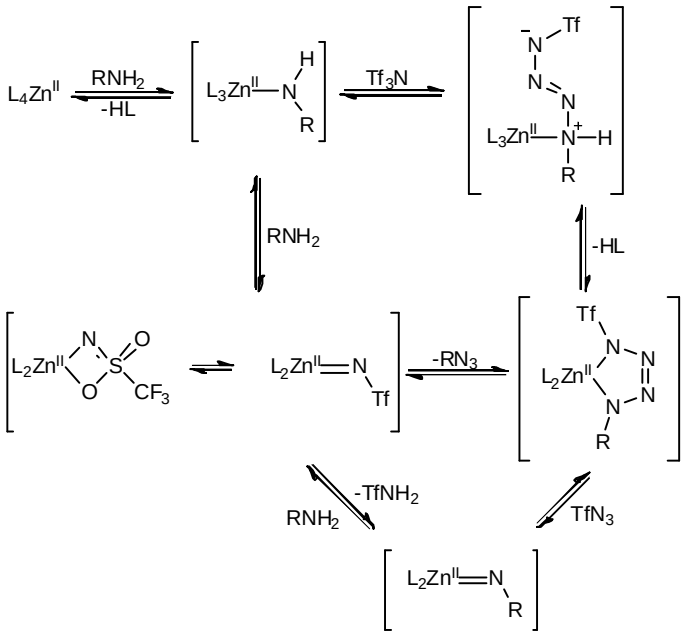


Scheme 39. Regitz diazotransfer reaction.

The second type of diazotransfer reaction converts an amino group into an azide, using triflic anhydride and sodium azide (triflic azide). Either aliphatic or aromatic amines (Liu & Tor 2003; Yan et al., 2005) can be transformed into azide groups, affording an amino surrogate which in turn, can be easily reduced to amines that have their configuration retained (Fischer & Anselme 1967; Cavender & Shiner 1972; Vasella et al., 1991). The change of solvent and addition of transition metal salts (e.g., Cu(II)) have increased the efficiency of this reaction (Alper et al., 1996). Although not obvious,

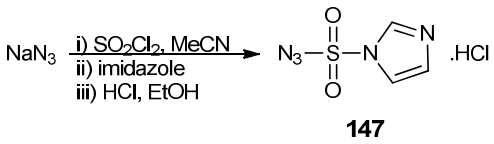
the reagents used in this reaction are extremely safe (previous reactions using dichloromethane (DCM) and sodium azide can be dangerous, with the formation of unstable diazidomethane (Conrow & Dean 2008).

The mechanism for this reaction still remains to be confirmed, although a dianionic tetrazene has been proposed as one of the key intermediates (Scheme 40) (Fischer & Anselme 1967; Nyffeler et al., 2002).



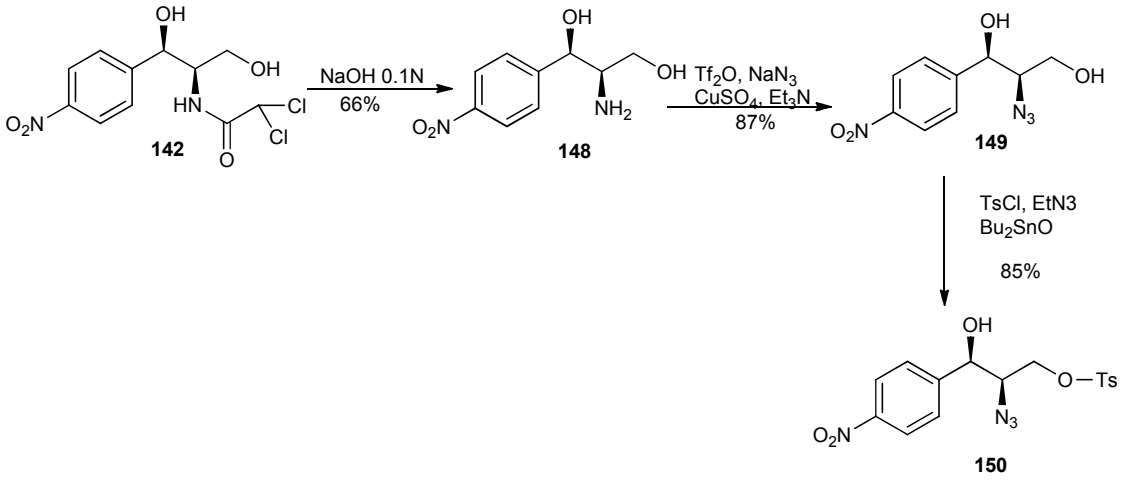
Scheme 40. Proposed mechanism of diazotransfer reaction.

More recently a new methodology for the diazotransfer reaction has been developed with the synthesis of an efficient, inexpensive and shelf stable reagent, imidazole-1-sulfonylazide hydrochloride (**147**) (Scheme 41) (Goddard-Borger & Stick 2007).



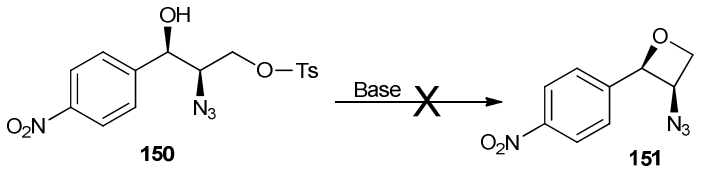
Scheme 41. Synthesis of imidazole-1-sulfonyl azide hydrochloride (147).

Synthetic approach 3 began with the hydrolysis of chloramphenicol (**142**) (Rebstock et al., 1949) with aqueous NaOH, which afforded the amino 1,3-diol product **148** in modest yields (Scheme 42). The amine was converted to the azide **149** through the use of triflic azide (generated *in situ* with triflic anhydride and sodium azide in anhydrous acetonitrile), copper sulfate and triethylamine in anhydrous acetonitrile. The product was selectively tosylated at the primary hydroxyl group with dibutyltin oxide and tosyl chloride (Martinelli et al., 1999), affording tosyl azide **150**.



Scheme 42. Synthesis of azido alcohols using chloramphenicol precursors.

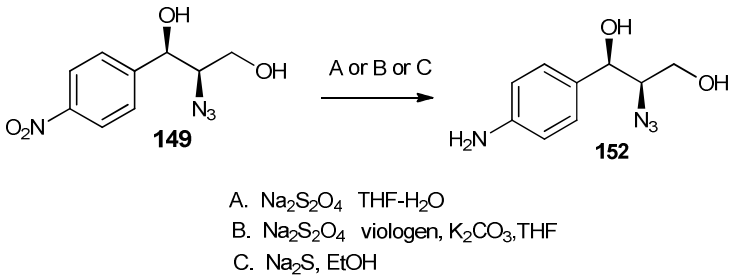
The tosyl azide **150** was reacted with potassium *tert*-butoxide, a standard reagent used for oxetane ring synthesis from precursor 3-hydroxy-1-tosylates. However, repeated attempts to form **151** from **150** resulted in the production of intractable mixtures of compounds. Examination of the literature revealed that the nitroaromatic ring could suffer vicarious nucleophilic substitutions when treated with potassium *tert*-butoxide to yield products carrying substituents on the *para* and/or *ortho* positions (Krylova et al., 2001); (Makosza & Podraza 2000); (Stalewski, 1998); (Makosza & Kwast 1998); (Makosza & Sienkiewicz 1998). This effect appeared to be limited to the nucleophilic *tert*-butoxide, so in an attempt to obviate this problem, we utilized several non-nucleophilic bases. Reactions performed with **150** in the presence of NaH or DBU failed to yield the desired oxetane **151** (Scheme 43). Therefore another strategy was conceived in order to avoid the undesired reactions that were provoked by the nitro substituent in the aromatic ring.



Scheme 43. Attempted synthesis of oxetanes from azido tosylate precursors.

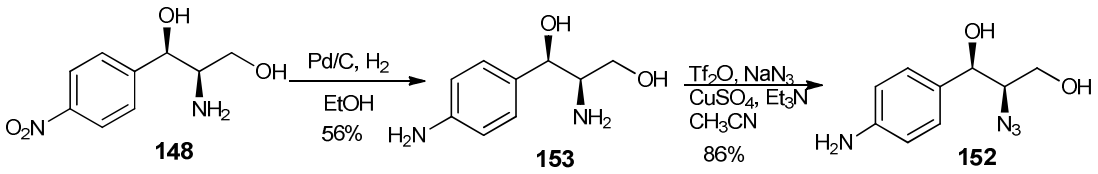
A logical choice was to reduce the nitro group to an amine after the diazotransfer reaction, and then make use of Sandmeyer reaction to manipulate the substituents in our favor. In other words, the reduction would have to be selective to aromatic nitro groups leaving the aliphatic azide intact. Several methods for selective reductions were

attempted, employing sodium bisulfite or sodium sulfide reducing systems (Park et al. 1993; Brouillette et al., 2003; Huber et al., 1988). Using literature conditions, reduction of **149** provided the desired aniline product **152**, in low yields, perhaps due to the difficulty associated with purification and product stability (Scheme 44).



Scheme 44. Selective reduction of nitroaromatics to anilines.

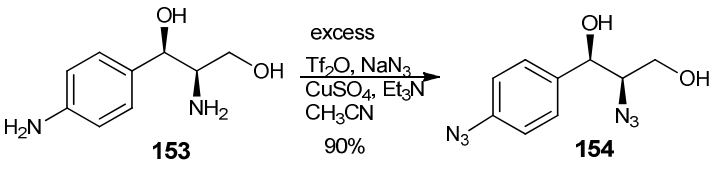
Since these reduction reactions were not effective, a modified approach was adopted, where the diazotransfer reaction would be applied to a molecule with two amino groups, hence the nitro group would need to be reduced at the beginning of the synthesis.



Scheme 45. Selective diazotransfer reaction.

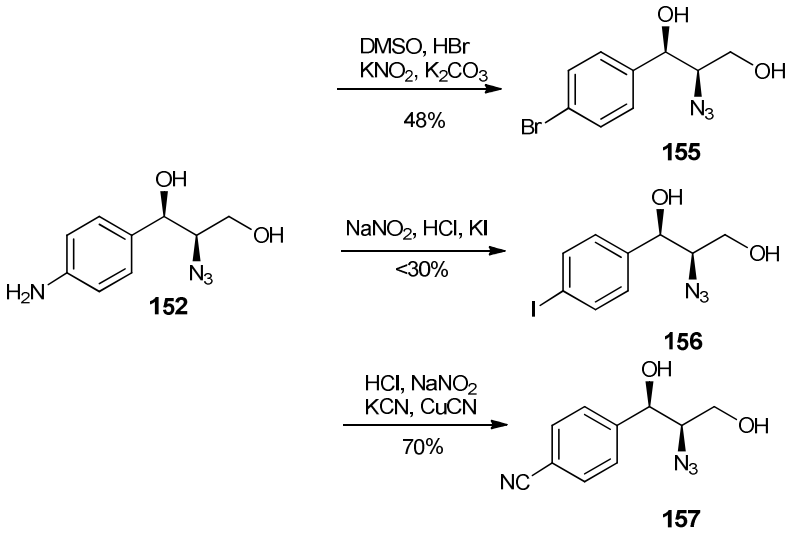
Treatment of the chloramphenicol hydrolysis product **148** under standard hydrogenation conditions (Pd/C; H_2; EtOH) yielded the aniline **153** (Scheme 45). The diazotransfer reaction was conducted on **153** using 1.1 equivalents of triflic azide (prepared *in situ* from triflic anhydride and sodium azide) in the presence of copper sulfate and triethylamine, resulting in the formation of aliphatic azide **152** in excellent

yield. To our surprise, the aliphatic amine has a preference over the aromatic amine regarding the diazotransfer reaction. Therefore it was possible, using the correct ratio between amino substrate and triflic azide, to selectively transform only the aliphatic amine into the azide, while sparing the aromatic amine. Additionally, the use of excess triflic azide results in the formation of the bis-azide product **154** (Scheme 46).



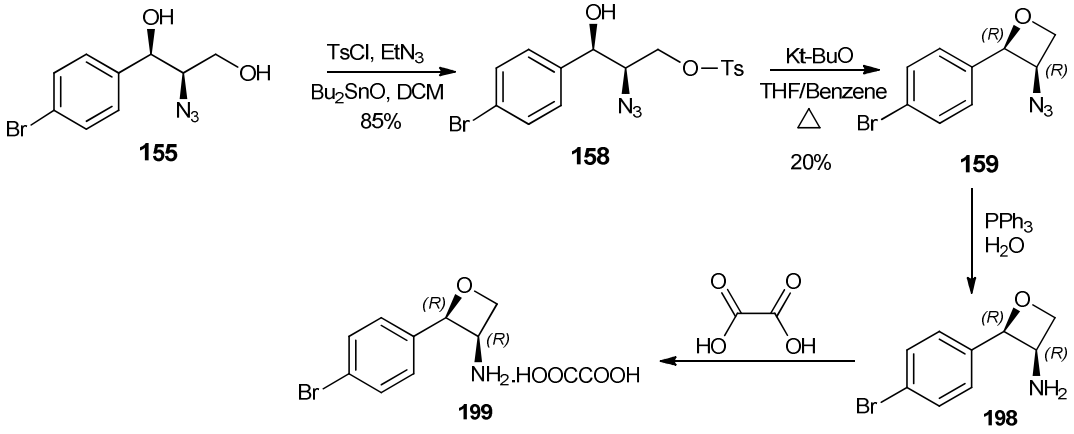
Scheme 46. Formation of bis-azide 154 from diazotransfer reaction of 153.

The success of the diazotransfer reaction then set the stage for a Sandmeyer reaction, where the aromatic amine in compound **152** would be converted to a bromide (**155**), iodide (**156**), and a nitrile (**157**) (Scheme 47). We used initially a variant of the Sandmeyer reaction, which employs a halodimethylsufonium halide formed *in situ* from a hydrohaloic acid and DMSO (in our case HBr) (Baik et al., 2005). This methodology proved beneficial, although the yields were not superior to the traditional Sandmeyer; the major drawback involved the product work-up protocols.



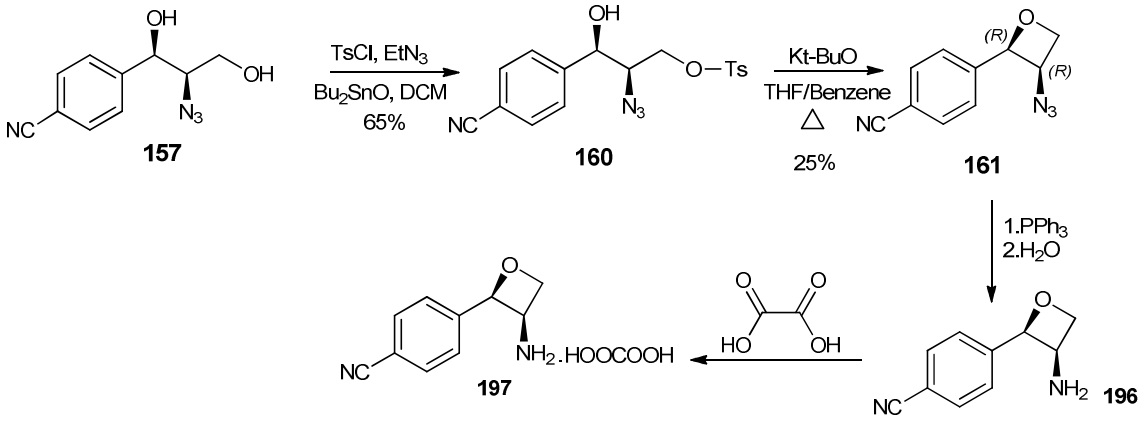
Scheme 47. Sandmeyer reactions of 152.

The use of the Sandmeyer reaction to produce both halogenated (Boojamra, 2003) and aromatic nitriles (Bühler et al., 2004) was conducted in order to take advantage of these functional groups in later coupling reactions. The Sandmeyer products (**155-157**) were characterized by MS evaluation and ^{1}H and ^{13}C-NMR spectroscopic analysis.

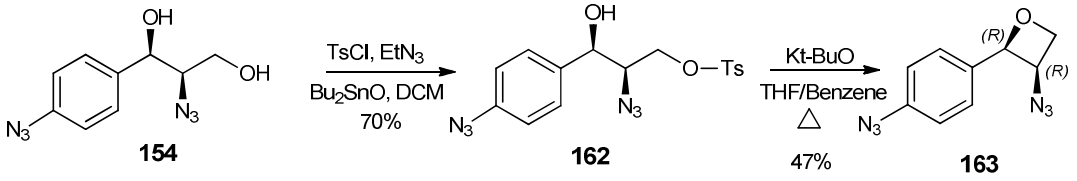


Scheme 48. Synthesis of (2*R*,3*R*)-3-azido-2-(4-bromophenyl)oxetane (159).

The bromo-azide derivative (**155**) was then subjected to a selective tosylation reaction under standard condtions yielding tosyl azide **158**; treatment with potassium *tert*-butoxide afforded (2*R*,3*R*)-3-azido-2-(4-bromophenyl)oxetane (**159**) in modest yields; **159** was reduced using Staudinger protocol followed by its conversion to an oxalate **199** (Scheme 48). The same set of reaction schemes were used for the synthesis of 4-((2*R*,3*R*)-3-azidooxetan-2-yl)benzonitrile (**161**) from tosyl azide **160**; later reduction of **161** using Staudinger conditions yielded 4-((2*R*,3*R*)-3-aminooxetan-2-yl)benzonitrile; the amino oxetane **196** was then converted in an oxalate salt (Scheme 49). The same set of reactions were employed for the synthesis of (2*R*,3*R*)-3-azido-2-(4-azidophenyl)oxetane (**163**), derived from tosyl azide **162** (Scheme 50).



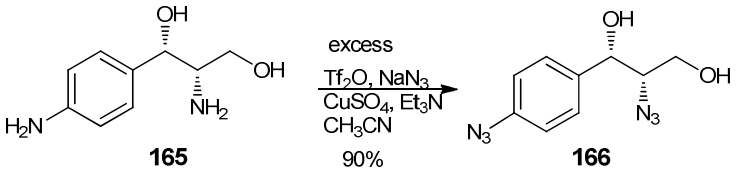
Scheme 49. Synthesis of 4-((2*R*,3*R*)-3-azidooxetan-2-yl)benzonitrile (161) and 4-((2*R*,3*R*)-3-aminooxetan-2-yl)benzonitrile (196).



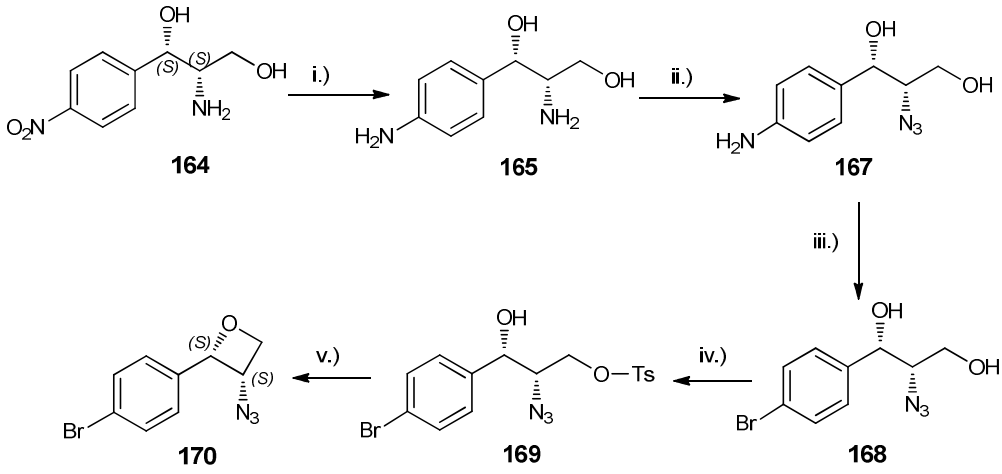
Scheme 50. Synthesis of (2*R*,3*R*)-3-azido-2-(4-azidophenyl)oxetane (163).

The use of potassium *tert*-butoxide in the cyclization reaction afforded low product yields due principally to competing reactions, in particular, elimination reactions. In an attempt to improve the yield of oxetane products in the cyclization reaction, a series of bases were treated with **162** to optimize the product yields. The use of $KN(TMS)_2$ (Toyota et al., 2000), *n*-BuLi (Ito, 1997), LDA (Saphier et al., 2004), KH (Sasaki et al., 1995), and KH (oil free)/18-crown-6 (Tino, 1987), and Cs_2CO_3 in DMF (Ameijde & Liskamp, 2003) failed to improve the yield of the oxetane product. Many of the reactions were performed in temperatures ranging from -78 ^oC to room temperature. It was later discovered that potassium carbonate (methanol solvent) was reported to function as an effective base in promoting 5-exo-*tet*-cyclization reactions, documented in the synthesis of the tetrahydrofuran-based natural product Jaspine B (Prasad & Chandrakumar 2007). Athough carbonate itself is not strong enough to abstract a proton from an alcohol, it has been documented that potassium carbonate and methanol generates substantial concentrations of CH_3OK *in situ* (Platonov et al. 2002). Treatment of **162** with potassium carbonate in methanol afforded a smooth conversion to the oxetane product **163** without the formation of elimination products. The disadvantage of this reaction is the slow rates of conversion; on average, reactions were completed in 5 days.

The successful synthesis of oxetanes derived from the chloramphenicol hydrolysis product prompted us to prepare the enantiomeric series of **159** and **161**. This was easily accomplished, since the requisite starting material (**164**) was commercially available. Scheme 49 depicts the five-step protocol for the synthesis of (2*S*,3*S*)-3-azido-2-(4-bromophenyl)oxetane (**169**). Also following the same procedure depicted on Scheme 46, the formation of the bis azide **166** was accomplished (Scheme 51). The overall yield of **169** was 13.5% from **164**.



Scheme 51. Formation of bis-azide 166 from diazotransfer reaction of 165.

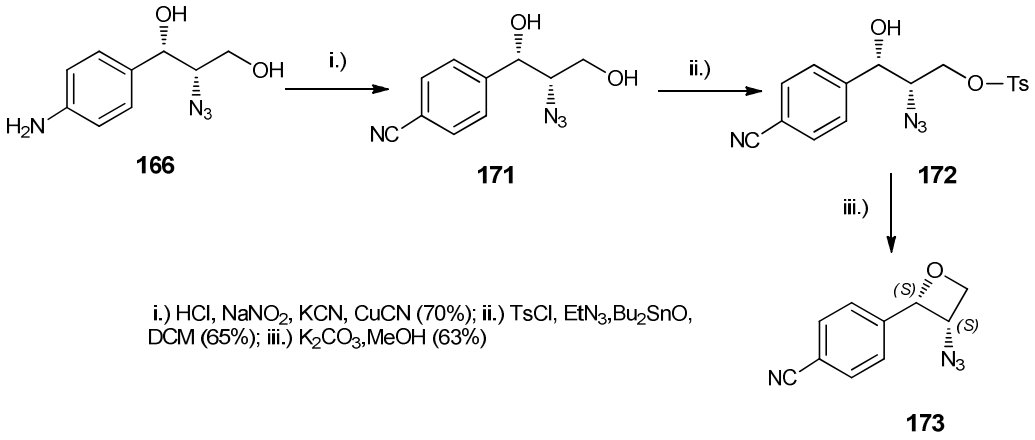


i.) Pd/C,1 atm. H_2, EtOH (56%); ii.)Tf_2O, NaN_3, $CuSO_4$, Et_3N, CH_3CN (86%); iii.) $NaNO_2$, HBr, CuBr (55%); iv.) TsCl, EtN_3,Bu_2SnO, DCM (85%); v.) K_2CO_3,MeOH (60%)

Scheme 52. Synthesis of (2*S*,3*S*)-3-azido-2-(4-bromophenyl)oxetane (170).

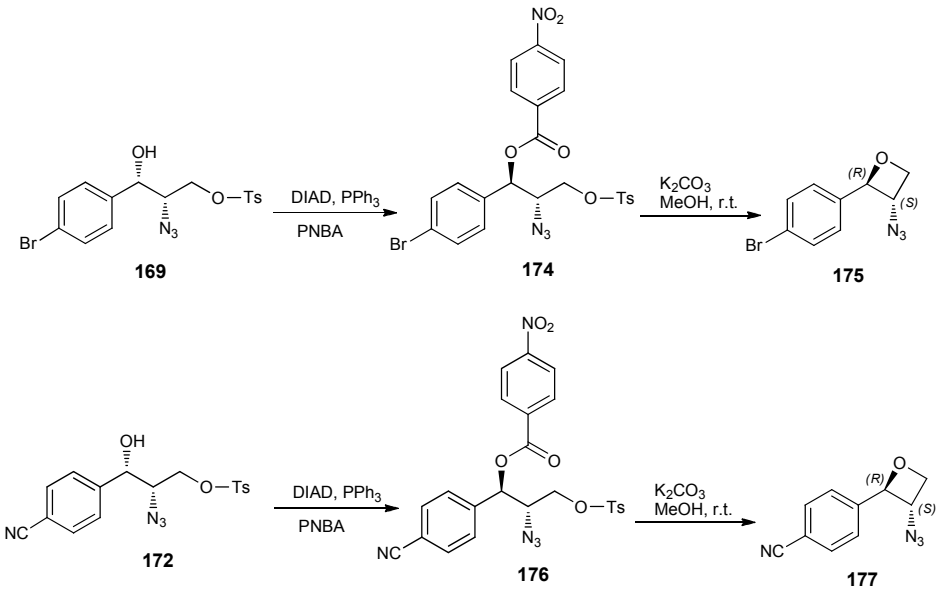
In a similar fashion, the nitrile Sandmeyer product **171** was converted to 4-((2*S*,3*S*)-3-azidooxetan-2-yl)benzonitrile (**173**) (Scheme 53). Final oxetane products and

intermediates were characterized by ^{1}H and ^{13}C-NMR analysis. Optical rotation data also confirmed that stereochemical integrity was preserved through the synthesis.



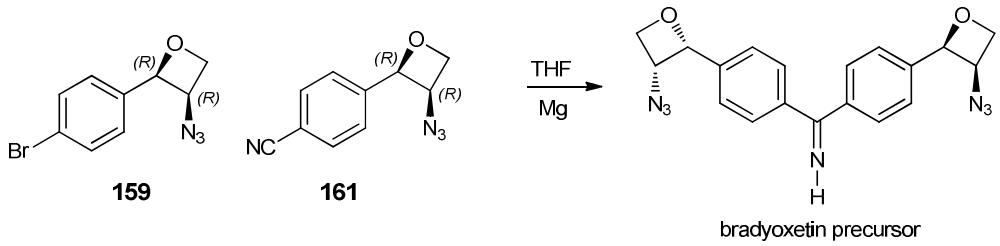
Scheme 53. Synthesis of 4-((2*S*,3*S*)-3-azidooxetan-2-yl)benzonitrile (173).

Mitsunobu reactions were employed as a means to invert the configuration of the carbon bearing the hydroxy group. This allowed for the expedient synthesis of the diastereomeric series of compounds. Briefly, 4-bromophenyl- and 4-cyanophenyltosyl azides (**169** and **172** respectively) were treated with DIAD, triphenylphosphine and p-nitrobenzoic acid. This afforded p-nitrophenyl esters **174** and **176**. Reaction of these esters with potassium carbonate in methanol afforded the oxetane products directly (via the initial ester hydrolysis and subsequent cyclization, Scheme 54). The products were characterized as (2*R*,3*S*)-3-azido-2-(4-bromophenyl)oxetane (**175**) and 4-((2*R*,3*S*)-3-azidooxetan-2-yl)benzonitrile (**177**).



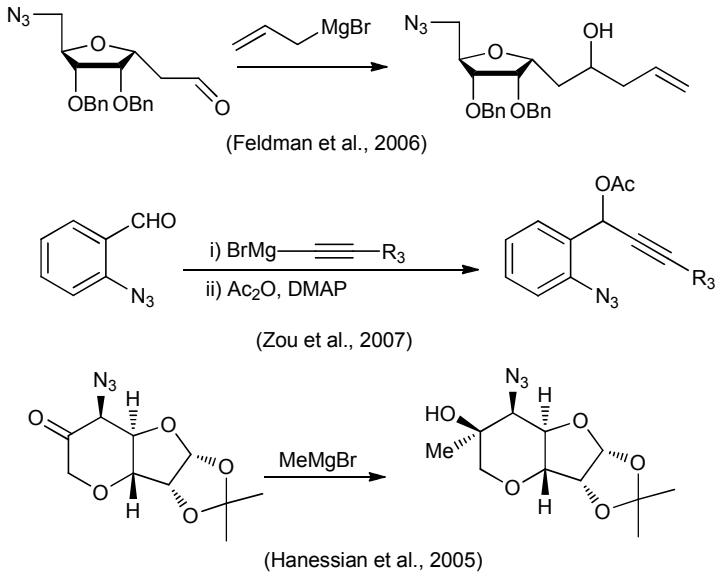
Scheme 54. Mitsunobu reactions in the synthesis of 175 and 177.

With the successful construction of oxetanes with defined stereochemical conformation and requisite functional groups, the next step was considered. It was envisioned that a Grignard reaction could be conducted by the reaction of magnesium with arylbromide **159** and subsequent reaction with nitrile **161**, leading to bradyoxetin precursor with defined stereochemical configuration about the oxetane ring (Scheme 55). If successful, this reaction would be applied to the other stereoisomeric sets of arylbromides and arylnitriles precursor oxetanes.



Scheme 55. Grignard reaction for bradyoxetin synthesis.

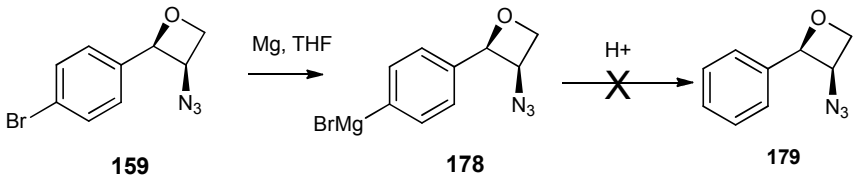
Consideration was given to the notion that the azide group may not be compatible under Grignard reaction conditions. However, several examples were identified in the literature which suggested otherwise (Scheme 56).



Scheme 56. Grignard reactions of organomagesium reagents to molecules containing an azide group.

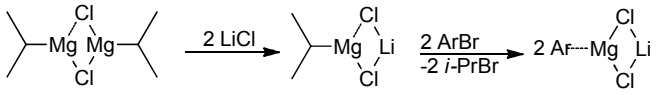
Reaction of oxetane **159** with magnesium in anhydrous THF was first investigated on a small scale to determine whether magnesium would insert and form a stable reagent

(e.g., **178**) to add to nitrile **161** and form the imine product (Fergus et al., 2004). Aliquots of the reaction mixture were taken at various time points, and quenched with dilute acid (Scheme 57). If the magnesium insertion was successful, (2*R*,3*R*)-3-azido-2-phenyloxetane (**179**) would have been produced. Unfortunately, this product was not identified in the reaction mixture.



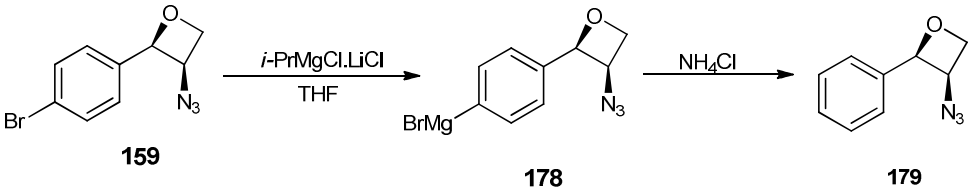
Scheme 57. Attempts at forming Grignard reagent 178.

Since the insertion of magnesium was not occurring, it seemed appropriate to look for a more robust method in the literature. An elegant solution was to catalyze the Grignard reaction with lithium salts, like LiCl. For example, reaction of 4-bromoanisole with *i*-PrMgCl (without additive) affords the magnesium insertion product in 18% yield, but the same reaction in the presence of the additive LiCl, the magnesium insertion product yield increases to 84% . The reaction is believed to proceed with the formation of a complex, *i*-PrMgCl-LiCl, which later catalyzes the Br/Mg exchange reaction (Scheme 58) (Krasovskiy & Knochel 2004).



Scheme 58. Catalysis of the Br/Mg exchange reaction with LiCl.

A solution of *i*-PrMgCl-LiCl complex (generated in situ by the addition of a solution of *i*-PrMgCl in THF to LiCl) was prepared, and a solution of (2*R*,3*R*)-3-azido-2-(4-bromophenyl)oxetane (**159**) was added dropwise and stirred at room temperature for 6 hours. Confirmation of the Mg insertion was established by quenching an aliquot of the reaction mixture with NH_4Cl, which yielded the "naked" phenyloxetane **179** (Scheme 59).



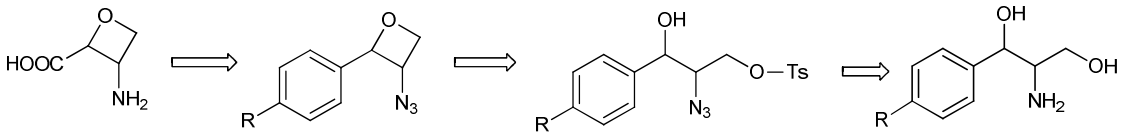
Scheme 59. Successful Mg insertion reactions using LiCl additives.

Once the magnesium insertion reaction was confirmed, the reaction was applied towards the synthesis of bradyoxetin, as depicted earlier in Scheme 55. However, no products were formed as a result of Grignard addition to the nitrile (recovered starting material). This reaction was repeated under a variety of conditions, with changes in solvent, temperature, and reaction time.

3.5 Approaches towards the synthesis of oxetin

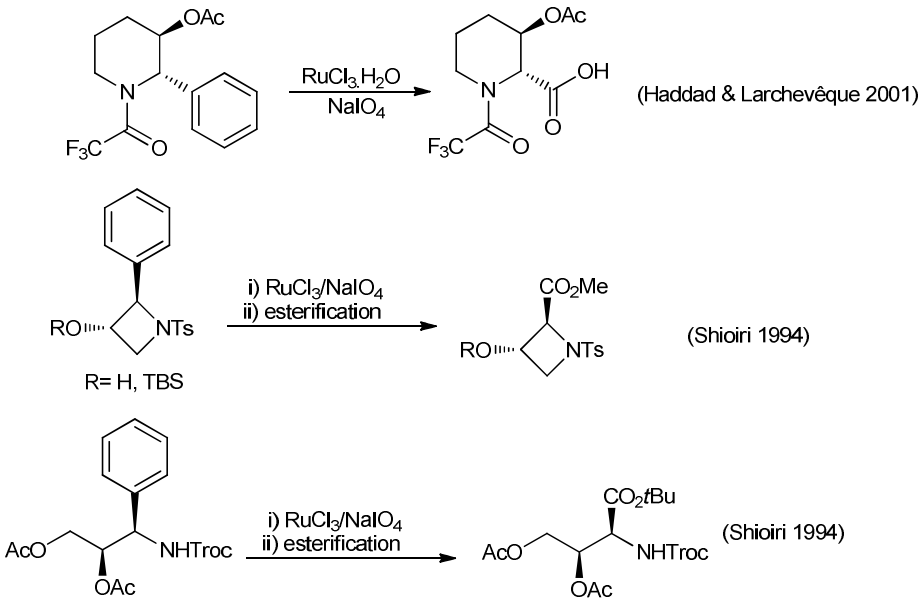
The lack of success in the final stages of bradyoxetin synthesis prompted us to examine approaches for the synthesis of other oxetane, namely, the oxetin series of compounds. This approach was based on the fact that aromatic rings can serve as

carboxylic acids precursors via oxidative degradation reactions in the presence of ruthenium salts (Scheme 60). We believed that a number of our "bradyoxetin" intermediates could be used for the direct synthesis of oxetin stereoisomers.



Scheme 60. Retrosynthetic strategy for the synthesis of oxetin (stereochemistry not defined).

Oxidative degradation of aromatic rings with ruthenium salts produce carboxylic acids with overall retention of configuration. Some examples that have successfully been employed in the oxidative conversion of aromatic rings to carboxylic acids are depicted in Scheme 61.



Scheme 61. Application of oxidative degradation reactions.

The $RuCl_3$ oxidizing system has been used successfully with a variety of aryl substrates including: 2-chloroquinoline (Cho et al., 2004), *p*-methoxybenzene (Burke & Voight 2000), 3,4-dimethoxybenzene (Kalvin & Woodard 1985), 2,5-dimethoxybenzene (Sarma & Chattopadhyay 1982), and acetylated anilines (Wu & Mosher 1986). Not all aromatic groups are suitable for degradation with Ru catalysts.

The mechanism of the oxidative decarboxylation reaction is illustrated in Figure 24. The first step for the initial cleavage of the aromatic double bond has been extensively documented. The Ru(VIII) is generated *in situ* by using a catalytic amount of $RuCl_3$ and $NaIO_4$ (generally added in a large quantity when compared to the stoichiometry). The Ru(VIII) is therefore constantly regenerated. The first product of the oxidation is the α–ketoaldehyde (**A**) which is subsequentially converted to the aldehyde hydrate (**B**) in aqueous media. The hydrate (**B**) is further oxidized to the keto acid (**C**), and undergoes a second hydration reaction leading to intermediate (**D**). Reaction with Ru(VIII) species leads to the obligatory pentacyclic ruthenium intermediate (**E**). Breakdown of this complex produces the product carboxylic acid (**F**) and loss of carbon dioxide (Bruckner, 2010).

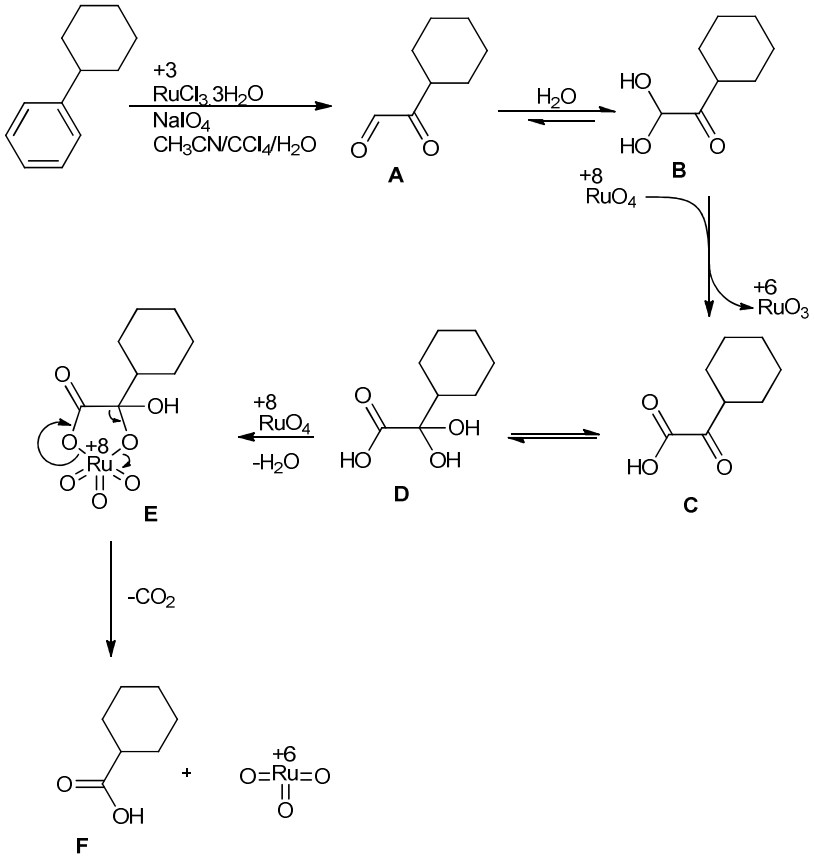
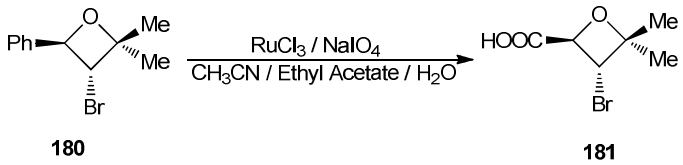


Figure 24: Proposed mechanism for oxidative cleavage of aromatic compounds with $RuCl_3$ and $NaIO_4$.

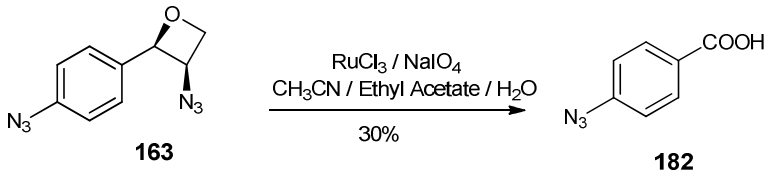
Similar oxidative degradation reactions have been reported for the synthesis of oxetane carboxylic acids (**181**), formed from the reaction of **180** with $RuCl_3/NaIO_4$ in CH_3CN/ethyl acetate/H_2O (Scheme 61) (Albert et al., 2001).



180 181

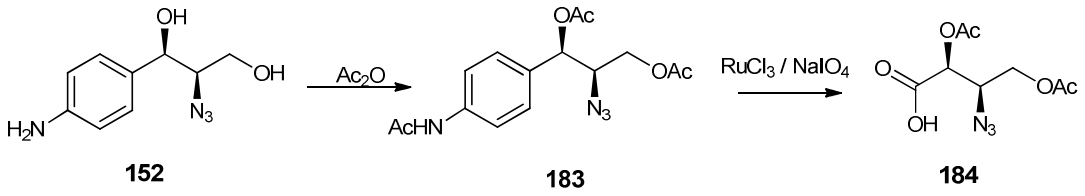
Scheme 62. Oxidative cleavage reaction of a 2-phenyl oxetane derivative.

Initially, we focused our attention to oxetanes that we produced as intermediates for the total synthesis of bradyoxetin. The first oxetane selected for the oxidative cleavage reaction was was (2*R*,3*R*)-3-azido-2-(4-azidophenyl)oxetane (**163**) (Scheme 63), since it was a side-product formed from a large scale diazotransfer reaction.



Scheme 63. Oxidative cleavage of oxetane 163.

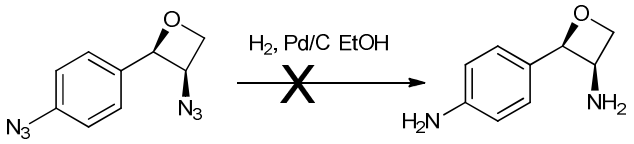
The result of the oxidative cleavage reaction was unusual, insofar as the only product isolated from the reaction mixture was 4-azidobenzoic acid (**182**). The oxidation reaction cleaved the oxetane ring rather than the aromatic ring. A survey of the literature shed light regarding this unusual oxidation; it appears that certain functional groups located on the aromatic ring are not suitable for oxidative degradation reactions. A pilot reaction with compound **152** (Scheme 64) was performed, by initially acetylating both the amino and hydroxyl substituent, affording **183**. This acetylated derivative was submitted to the oxidative cleavage reaction using $RuCl_3/NaIO_4$. In this example, the oxidative cleavage reaction was successful, clearly substantiating the influence of functional group effects on the aromatic ring.



152 183 184

Scheme 64. Oxidative cleavage reaction of 182 with $RuCl_3$ and $NaIO_4$.

The next logical step was to convert the 4-azido oxetane **163** into the 4-amino oxetane **185** by catalytic hydrogenation (Scheme 65). Monitoring of the reaction progress by TLC and MS evaluation suggested that **185** was being formed during the hydrogenation reaction. However, attempts at isolating **185** from the reaction mixture failed; a black intractable material was formed upon repeated attempts, possibly due to the 4-amino groups participation in oxetane ring opening reactions.

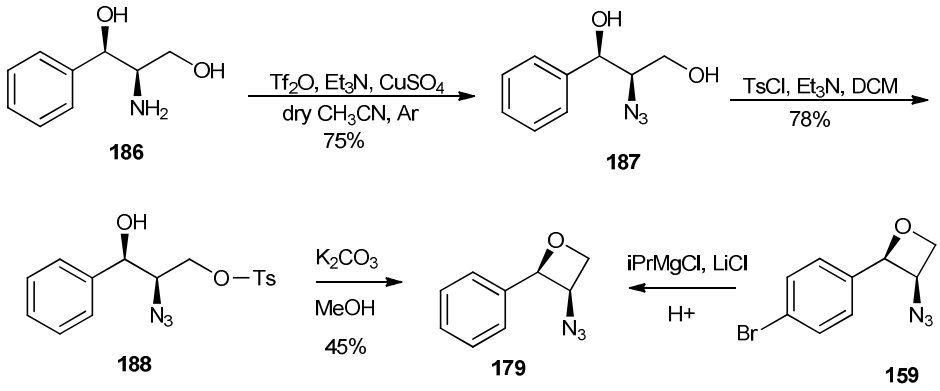


163 185

Scheme 65. Attempted reduction of bis-azide 163.

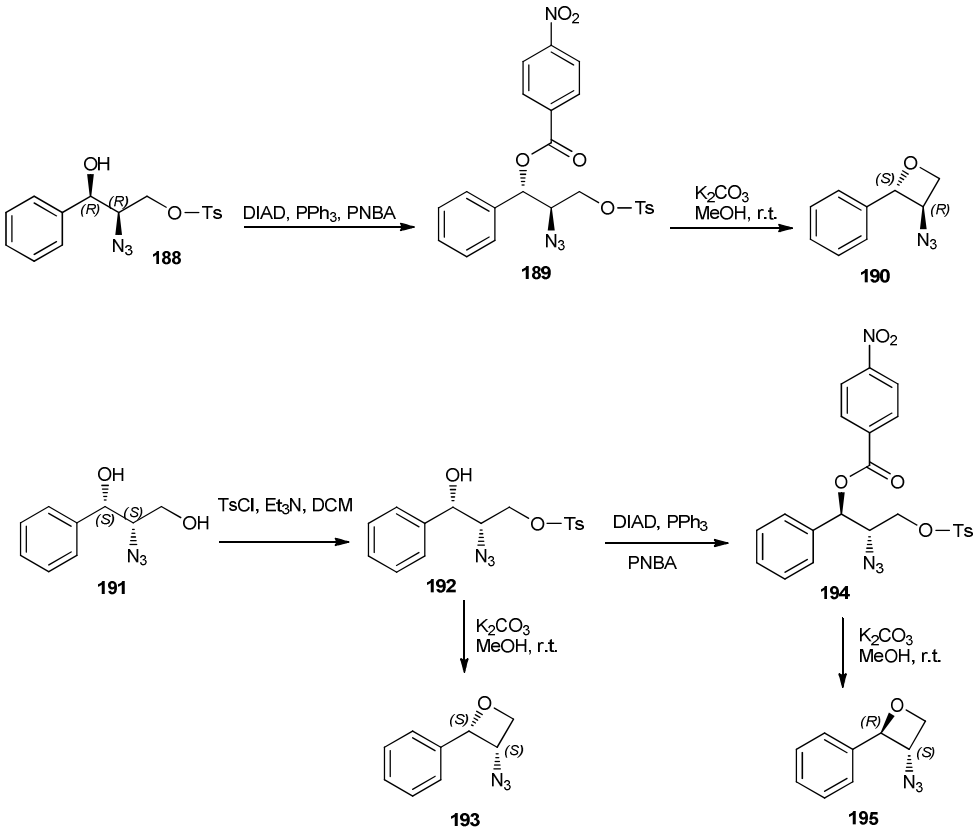
A second option for the production of oxetin stereoisomers using the oxidative cleavage reaction invoked the use of oxetanes bearing an unsubstituted aromatic ring. To our favor, the amino diol lacking functionality on the aromatic ring (compound **186**) had become commercially available for the first time. Compound **185** was subjected to the same set of reaction protocols that we developed for bradyoxetin intermediates (Scheme 65). Briefly, a diazotransfer reaction afforded **186**, selective tosylation yielded **187**, and cyclization with potassium carbonate in methanol generated (2*R*,3*R*)-2-phenyloxetan-3-

amine (**187**) (the same compound produced during our investigation of the magnesium insertion reaction with arylbromide oxetane **159**). Cyclization reactions of **188** using potassium *tert*-butoxide failed to produce oxetane **179**, and instead, afforded elimination products.



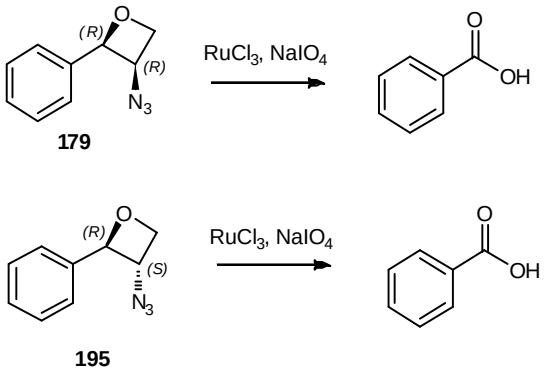
Scheme 66. Synthesis of (2*R*,3*R*)-2-phenyloxetan-3-amine (179).

Reaction protocols were repeated for the synthesis of the remaining isomers of 2-phenyloxetan-3-amine (**190**, **193**, and **195**) (Scheme 67). Since Mitsunobu reaction conditions require the use of triphenylphosphine (**188** to **189** and **190** to **194**), it was imperative that the PPh_3 was completely reacted with the DIAD reagent, since PPh_3 reacts with azides in the Staudinger reaction to form iminophosphoranes (Solsona et al., 2003).



Scheme 67. Synthesis of chiral 2-phenyloxetan-3-amines.

2-phenyloxetan-3-azides **179** and **195** were submitted to oxidative cleavage reactions using $RuCl_3/NaIO_4$ in acetonitrile/water (Scheme 68). The only product isolated from the reaction mixture was benzoic acid.



Scheme 68. Oxidative cleavage reactions of 2-phenyloxetan-3-amines.

3.6 Conclusions

This research describes the evolution on the understanding of some of the quorum sensing pathways and how some of chemical signals can, in different species, trigger different phenotypic responses. The objectives were tailored to synthetic chemistry approaches, with the purpose of elucidating the absolute configuration of bradyoxetin.

Regarding conclusions concerning the stereochemistry of bradyoxetin, further experiments are required, but several insights into the possible relative configuration of the structures can be inferred. The reported coupling constants obtained from evaluation of the ^{1}H NMR spectrum between H1 and H2 of bradyoxetin is 2.95 Hz (Loh et. al., 2002) while the coupling constants for the same set of protons in compound **196** is 6.8 Hz. It appears that the imine bridge between the aromatic rings exerts a larger influence on the protons H1 and H2 than anticipated. The azido oxetanes do not differ to a large extent when comparing the coupling constants from the amino oxetanes. The difference between **161** and **196** was only 0.1 Hz. The synthesized oxetanes offer a better model for the evaluation than the oxetanes described in the seminal article. They possess a closer structure than the ones obtained through Paterno-Buchi, which lack a para-substituent and possess an amide rather than an amine or an azide; their coupling constants are on the order of 7Hz. *Trans*-substituted oxetanes possess smaller coupling constants when

compared to *cis*-substituted analogs; the values are still large compared to bradyoxetin.

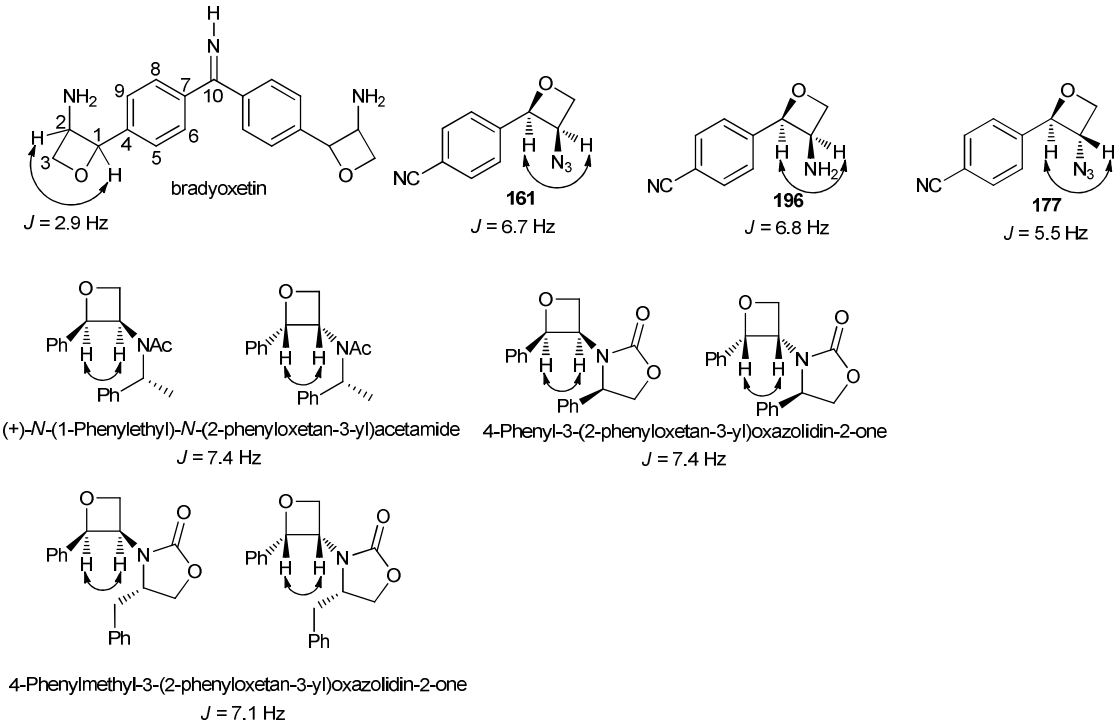


Figure 25. Oxetanes and their coupling constants

Some new insights into oxetane synthesis have been achieved and a new option has been disclosed for using chloramphenicol and its derivatives as chiral building blocks. Approaches were also developed for the synthesis of the natural product oxetin, using aromatic rings as carboxylic acids surrogates with retention of configuration. Although the completion of both bradyoxetin and oxetin was not achieved, an efficient route for the synthesis of oxetin has proposed and nearly accomplished, and a new synthesis of bradyoxetin has been proposed and its total synthesis is on the horizon. It has been also determined that aliphatic amines are more prone to diazotransfer than aromatic amines. The inverse was also tested, with aromatic azides being selectively reduced in the presence of aliphatic azides.

The future of this research can surely be expanded with the investigation of 2-phenyl-3-amino oxetanes as CNS agents, since they share a striking resemblance with katinone, methamphetamine and other derivatives such as bupropion. The methylation of the amine can be achieved by following a protocole described in the literature (Sayyed & Sudalai, 2004).

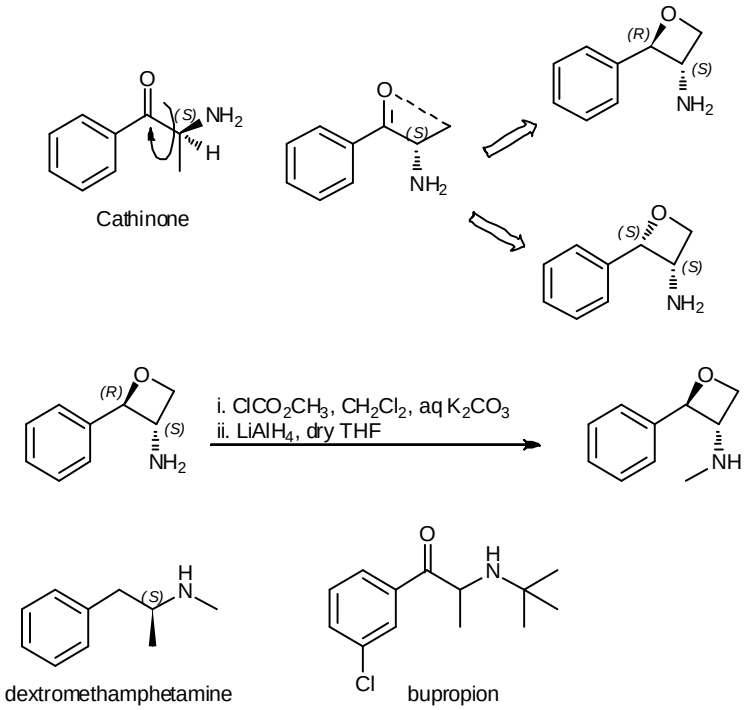
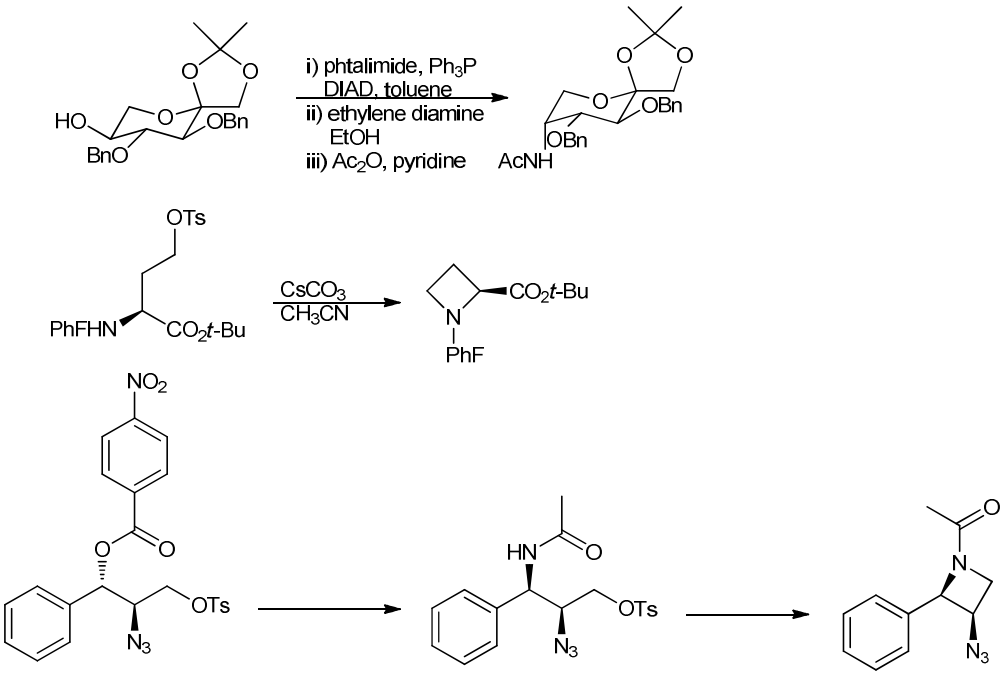


Figure 26. Proposed methylation of aminooxetanes and rationale based on cathinone.

The intermediates obtained through Mitsunobu reaction also can be easily manipulated with a suitable nucleophile to diversify the construction of hetereocycles other than oxetanes. As an example, azetidines can be obtained as demonstrated in the prior literature (Tatibouet et al., 2001; Sajjadi et al., 2001).



Scheme 69. Proposed synthesis of azetidine derivatives based on Mitsunobu intermediates.

By providing a cheaper and shorter route to oxetin, the investigation of oxetin as an amino acid surrogate in oligopeptides that carry serine, as an example, would be feasible. The study of bradyoxetin on quorum sensing systems other than rhizobium, as well as the study of bradyoxetin fragments on such pathways is worthy of pursuit.

Some of the challenges met in this dissertation research should be considered as opportunities for future research. The regiocontrol of epoxide opening, stereocontroled bromonium mediated reactions, and a comprehensive study on aromatic oxidative degradation are ripe for study.

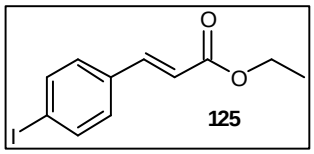
CHAPTER 4: EXPERIMENTAL

4.1 General Methods

All commercially available starting materials and reagents were purchased from Sigma-Aldrich (St. Louis, MO) unless otherwise noted. THF and diethyl ether were distilled from sodium-benzophenone ketyl. Analytical TLC plates (silica gel) were purchased from Sorbent Technologies (G Series-UV 254). Silica gel column chromatography was conducted using standard chromatography grade silica gel, 20-63 μM particle size, (Sorbent Technologies). Analytical TLC plates (alumina-B F-254-200 micron plates) were purchased from Selecto Scientific. ^{1}H NMR and ^{13}C NMR spectra were recorded at either 400 or 500 MHz on a Bruker Avance DRX spectrometer. The 2D NMR COSY, HMBC, HMQC, and NOESY were recorded at 500 MHz (Bruker Avance DRX) or 600 MHz NMR (Varian). Elemental Analysis was obtained using a PerkinElmer 2400 Series II CHNS/O Analyzer. Low-resolution mass spectrometry analysis was performed using a Waters ZQ single-quadrupole system using either ESI positive (ESI+) or ESI negative (ESI-) electrospray ionization. High-resolution mass spectrometry (HRMS) was recorded using a Micromass Q-TOF micro instrument. HPLC analysis was conducted with a Waters Delta Prep 4000 System with 7725I Rheodyne injector and Water 2487 Dual Wavelength Absorbance Detector. FTIR were measured using a Bruker Vector 33 system. Optical rotations were obtained with a Rudolph Autopol IV polarimeter at λ=589 nm.

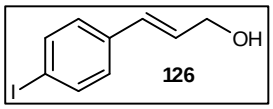
4.2 Synthetic Procedures and Compound Data

Ethyl *(E)*-4-iodo cinnamate (125). Ester **125** was prepared from 4-iodobenzaldehyde (**123**, 1.00 g, mmol) and carbethoxymethylene triphenylphosphorane (**124**, 1.8 g, mmol) in benzene, under reflux for 4 hours on a RBF. After the reaction was completed the solvent was evaporated and the residue was purified using silica gel column chromatography (95% hexanes-5% EtOAc) to yield **125** (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 2H, *J* = 8.5Hz), 7.57 (d, 1H, *J* = 16Hz), 7.23 (d, 2H, *J* = 8.5Hz), 6.42 (d, 1H, *J* = 16Hz), 4.25 (q, 2H, *J* = 7.1Hz), 1.33 (t, 3H, *J* = 7.1Hz).



125

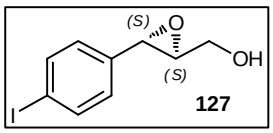
(*E*)-3-(4-Iodophenyl) prop-2-en-1-ol (126). A solution of ethyl *(E)*-4-iodo cinnamate (**125**, 8.24 g, 27.2 mmol) in anhydrous CH_2Cl_2 (100 mL) was treated with *i*-Bu_2AlH (82 mL, 1.0 M hexane solution, 82 mmol, 3.0 equiv) in three portions at -78^{o}C , and the mixture was stirred at -78^{o}C for 20 min. The reaction mixture was quenched by the addition of CH_3OH (25 mL), warmed to 25^{o}C, diluted with saturated aqueous sodium potassium tartrate (100 mL), and partitioned. The aqueous phase was extracted with CH_2C1_2 (4 X 100 mL), and the combined organic layers were washed with saturated aqueous sodium potassium tartrate (150 mL), dried over Na_2SO_4, and concentrated *in vacuo.* Flash chromatography (silica gel, 5 X 20 cm, 20-40% EtOAc-hexane) afforded **126** (7.07 g, 95%) as a white crystalline solid: mp. 108-110 ^{o}C (1:2 EtOAc-hexane, white needles); ^{1}H NMR ($CDC1_3$, 400 MHz) δ 7.63 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), δ 7.10 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-



126

H), δ 6.53 (d, 1H, J=15.8Hz, C3-H), 6.36 (dt, lH, J=5.4, 15.8 62.5 MHz) ^{13}C NMR ($CDC1_3$, 101 MHz) δ 137.7, 136.2, 129.9, 129.4, 128.2, 92.9, 63.5; IR (neat) *v*-3310, 2926, 2847, 1651, 1478, 1395, 1084, 1060, 1006, 971, 848, 799, 774 cm^{-1}.

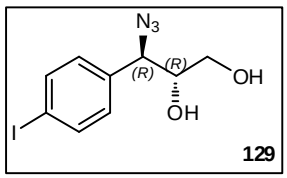
(2*S*,3*S*)-2-(Hydroxymethyl)-3-(4-iodophenyl)oxirane (127).



127

A solution of **126** (7.49 g, 26.0 mmol) in anhydrous CH_2C1_2 (250 mL) containing activated powdered 4-A molecular sieves (25 g, 1 g/mmol) was treated sequentially with (+)-diisopropyl L-tartrate (457 mg, 1.9 mmol, 0.41 mL, 0.075 equiv) and Ti(O-*i*-Pr)$_4$ (314 mg, 1.30 mmol, 0.33 mL, 0.05 equiv) at -20^{o}C (30 min). After reagent aging was complete, t-BuOOH (3.5 M CH_2Cl_2 solution, 52.0 mmol, 14.9 mL, 2.0 equiv) was added dropwise (15 min). After 4 h, the mixture was warmed from -20 to 0 ^{o}C (20 min), quenched by the addition of H_2O (25 mL), and allowed to warm to 25^{o}C (45 min). Aqueous NaOH (25%) (20 mL) was added and the mixture stirred at 25^{o}C (45 min). Following the addition of CH_3OH (10 mL), the aqueous phase was extracted with CH_2Cl_2 (3 X 50 mt), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 20-50% EtOAc-hexane) afforded **127** (3.21 g, 45%) as a white solid. mp. 80-82 ^{o}C. $[\alpha]^{25}_D$ -39.0 (c=1.0, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, 2H, *J* = 8 Hz, Ar C3- and C5-H), 7.02 (d, 2H, *J*=8 Hz, Ar C2-and C6-H), 4.03 (ddd, 1H, *J*=2.0 12.9 Hz, C1-H), 3.88 (d, 1H, *J*= 5.1 Hz, C3-H), 3.80 (ddd, 1H, *J* = 3.6, 7.6, 12.9 Hz, C1-H), 3.16 (m, 1H, C2-H), 1.85 (t, 1H, *J* = 6.2 Hz, OH); ^{13}C NMR ($CDC1_3$, 101 MHz) δ 137.63, 136.53, 127.57, 93.72, 62.39, 61.00, 55.0.

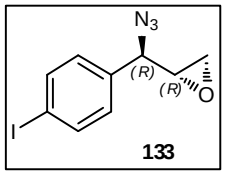
(2*R*,3*R*)-3-azido-3-(4-iodophenyl)propane-1,2-diol (129).



1786 mg of epoxide **126**, NaN_3 (4.14 g) and NH_4Cl (1.53 g) were dissolved in MeOH (12 ml) and water (2 ml) and heated to 112 ^oC, until the reaction was complete (the reaction was monitored using TLC). The reaction mixture was evaporated and the residue was extracted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (isocratic diethyl ether:petroleum ether) [9:1]. (Yellow oil, yield 78%) $[\alpha]^{25}_D$ -187.20 (c=1.0, $CHCl_3$). IR ($CHCl_3$):ν 3385, 2930, 2104, 1647, 1587, 1541, 1485, 1400, 1249, 1040, 814, 453 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, 2H, *J* = 8 Hz, Ar C3- and C5-H), 7.08 (d, 2H, J=8 Hz, Ar C2-and C6-H), 4.52 (d, *J* = 6.8 Hz, 1H), 3.75 (s, 1H), 3.59 (m, 2H), 2.72 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 62.84, 66.49, 73.88, 94.62, 129.68, 135.84, 138.08. ESIMS+; 342 (M^++ 23), 661 ($2M^+$+ 23).

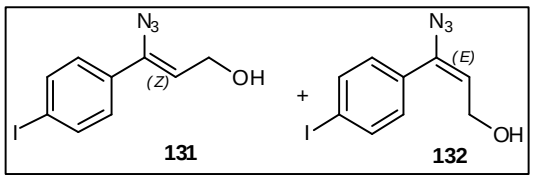
Reaction of tosyl derivative 130 with KOtBu Potassium *tert*-butoxide (0.6 g) was slowly added to a solution of the tosylate **130** (1.8 g) in anhydrous DCM at 0^oC. The reaction was monitored by TLC (70% diethyl ether: 30% petroleum ether). After completion the reaction was quenched with water. The organic phase was extracted with DCM and dried over Na_2SO_4. The organic phase was then separated and evaporated. Purification of two product bands **131/132** (mixture) and **133** was accomplished using silica gel chromatography (gradient of diethyl ether:petroleum ether [5:95to 50:50].

(*R*)-2-((*R*)-azido(4-iodophenyl)methyl)oxirane (133) $[\alpha]^{25}_{D}$ - 132.20 (c=1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76 (d, J = 8.5Hz, 2H), 7.13 (d, J = 8.5Hz, 2H), 4.57 (d, J = 4.5 Hz, 1H), 3.23–3.21 (m, 1H), 2.88-2.85 (m, 1H); ^{13}C NMR (CDCl3, 101 MHz): δ 44.83, 53.61, 64.70, 94.62, 129.17, 135.53, 138.03. FTIR ($CHCl_3$) ν 2103, 1647, 1587, 1541, 1486, 1398, 1296, 1061, 837, 452 cm^{-1}; ESIMS (+): 301(MH^+).

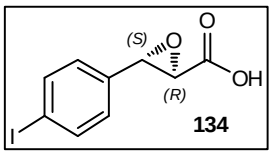


133

(*Z*)-3-azido-3-(4-iodophenyl)prop-2-en-1-ol (132) and (*E*)-3-azido-3-(4-iodophenyl)prop-2-en-1-ol (131) (Major *E* isomer listed). ^{13}C NMR (CDCl3, 100 MHz): 58.16, 95.20, 118.83, 128.74, 130.73, 133.85, 138.01.



Attempted synthesis of (2*R*,3*S*)-3-(4-iodophenyl)oxirane-2-carboxylic acid (134)



Method 1. To a vigorously stirred mixture of the epoxy alcohol **127** (276 mg, 1 mmol) in 2 mL of carbon tetrachloride, 2 mL of acetonitrile, and 3 mL of water was added sodium bicarbonate (0.42 g; 5 mmol), and sodium periodate (0.642 g ,3 mmol). Ruthenium trichloride trihydrate (7.5 mg, 33 μmol) was then added. The mixture was stirred at 20 ^{o}C for 44 h, after which the acidic material was extracted at 0 ^{o}C carefully into diethyl ether and the organic layer dried over sodium sulfate. The ethereal fraction

was submitted to acid-base work up. No oxidation product was detected by either ESI(-)-MS or ^{13}C-NMR analysis.

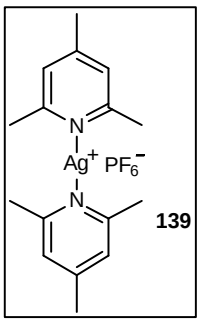
Method 2. Ruthenium trichloride trihydrate (0.0075 g, 33 μmol) was added to a stirring biphasic mixture of epoxy alcohol **127** (0.15 g, 1 mmol), sodium periodate (0.642 g, 3 mmol), and sodium bicarbonate (0.42 g, 5 mmol) in CCl_4 (2 mL), acetonitrile (2 mL), and water (3 mL). After 42 h of stirring, an additional quantitity of $RuCl_3$ (0.0076 g, 34 μmol) and sodium periodate (0.157 g, 0.72 mmol) were added and the stirring was continued for 1 h to complete the reaction. Then, DCM (8 mL) was added followed by a small amount of water (until phase separation occurred). The pH of the water layer was adjusted to 4.0 and the aqueous layer was extracted with DCM. Acidification and extraction were repeated until the pH remained constant. The combined layer was dried over Na_2SO_4 and solvent evaporated. No oxidation product was detected by either ESI(-)-MS or ^{13}C-NMR analysis.

Method 3 A solution of **127** (250 mg, 0.90 mmol) in anhydrous DMF (4.0 mL) was treated with PDC (1.10 g, 2.87 mmol, 3.5 equiv) at 25 ^{o}C. After 5 h, additional PDC (348 mg, 0.90 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 25 ^{o}C for an additional 5 h before the addition of H_2O (50 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (4 X 50 mL), and the combined organic layers were washed successively with H_2O (3 X 75 mL) and brine (3 X 75 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was dissolved in saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (10 mL). The organic phase was further extracted with saturated aqueous $NaHCO_3$ (3 X 10 mL), and the combined aqueous layers were acidified to pH 4 with the addition of 5% aqueous HCl and extracted with EtOAc (4

X 20 mL). The combined organic phase was washed with H_2O (3 X 20 mL) and saturated aqueous NaCl (3 X 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. No oxidation product was detected by either ESI(-)-MS or ^{13}C-NMR analysis.

Method 4. A stock solution of H_5IO_6/CrO_3 was prepared by dissolving H_5IO_6 (11.4 g, 50 mmol) and CrO_3 (23 mg, 1.2 mol %) in wet MeCN (0.75 v % water) to a volume of 114 mL (complete dissolution typically required 1-2 hours). The H_5IO_6/CrO_3 solution (11.4 ml) was then added to a solution of the alcohol **127** (2.0 mmol) in wet acetonitrile (10 mL, 0.75 v % water) in 30-60 minutes while maintaining the reaction temperature at 0-5 °C. The mixture was aged at 0 °C for 0.5 h and the completion of the reaction was confirmed by ESIMS. The reaction was quenched by adding an aqueous solution of Na_2HPO_4, (0.60 g in 10 mL of H_2O). Ethyl acetate was added and the organic phase was submitted to acid-base work-up. The organic layer was separated and dried over Na_2SO_4. No oxidation product was detected by either ESI(-)-MS or ^{13}C-NMR analysis.

Bis(2,4,6-trimethylpyridine)silver(I) hexafluorophosphate (139).

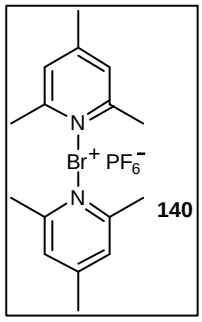


139

A 2-L, three-necked, round-bottomed flask was equipped with a mechanical stirrer and a 250-mL pressure-equalizing dropping funnel. The flask was charged with 1 L of distilled water, 100 g of silver nitrate (0.588 mol) and 109.3 g of potassium hexafluorophosphate (0.594 mol) When all the solids were dissolved, 221 mL of 2,4,6-collidine (1.67 mol) was added over 10 min with stirring. Technical grade 2,4,6-collidine can be used after purification by distillation from calcium hydride CaH_2. A slight exothermic reaction was observed,

corresponding to the formation of a white solid. The mixture was stirred for 1 hr at room temperature, the solid was suction filtered, and the filter cake was washed with 1 L of water. The solid was dried in the dark in a desiccator under high vacuum over phosphorus pentoxide (P_2O_5) for 1 week, to afford 262 g (90%) of the silver salt as a white-gray solid, mp. 210°C.

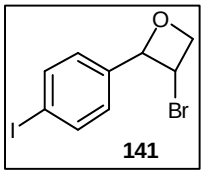
Bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophosphate (140).



140

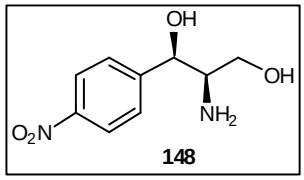
A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a 50-mL pressure-equalizing addition funnel, and a drying tube containing calcium chloride was charged with 500 mL of dry DCM, and 82.5 g of bis(trimethylpyridine)silver(I) hexafluorophosphate (**139**, 0.166 mol). Then, 8.3 mL of bromine (0.161 mol) was added over a period of 10 min. The mixture was stirred until all the bromine was consumed (1 hr) [Note: all of the bromine should be consumed before removal of the solvent]. The resulting yellowish solid (silver bromide) is suction filtered and washed with 100 mL of anydrous DCM. The filtrate was concentrated on a rotary evaporator at a maximum bath temperature of 30°C to give 65 g (83%) of bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophosphate (**140**) as a white solid (mp. 127-128°C). This solid must be stored in the dark at 0°C.

3-bromo-2-(4-iodophenyl)oxetane (141). To bis(collidine)bromine(I) hexafluorophosphate (**140**, 0.71 g, 1.5 mmol) in DCM (30 mL) was added a solution of allylic alcohol **126** (1.2 mmol) and 2,4,6-collidine (0.15 g, 1.2 mmol) in DCM (10 mL) over 6 h. Subsequently, silica gel (2 g) was added and the solvent was removed. The product was purified by flash chromatography over silica gel using an initial gradient of petroleum ether 100% which was increased to diethyl ether 20%-petroleum ether 80% affording oxetane **141** as an oil (6% yield) ^{1}H NMR: δ 3.92 (dd, *J* = 7.6 Hz, 1H); 4.26 (m, 1H), 4.47 (dd, 1H), 4.75 (d, 10 Hz, 1H), 7.72 (d, *J* = 8 Hz, 2H), 7.16 (d, *J* = 8 Hz, 2H). ^{13}C NMR: δ 42.90, 76.34, 91.38, 94.60, 127.00, 137.88, 138.208.



141

(1*R*,2*R*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol (148). Chloramphenicol (**142**) (3.0 g) was treated with 200 mL of 0.1 M aqueous NaOH at room temperature for 18 h. The solution was filtered and the white solid was washed with water and dried over P_2O_5 (high vacuum) yielding hydrolysis product **148** (mp.161-162 ^{o}C): $[\alpha]^{25}_{D}$ -23.3^{o} (c=3.0, MeOH). Literature reported melting point and optical rotation are both in agreement with our synthesized compound.



148

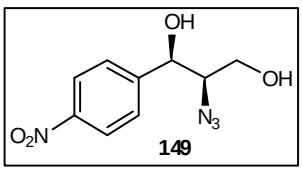
General procedure for diazotransfer reactions.

A typical experimental procedure for the preparation of triflyl azide was as follows: a suspension of sodium azide (436 mg, 6.70 mmol) in 8 mL of acetonitrile (pyridine) was

cooled in ice bath. Triflic anhydride (1.57 g, 5.56 mmol) was added by syringe at 0 ^{o}C over a 5 minute period. The reaction was stirred for 2 h at 0 ^{o}C , and the TfN_3- solution (filtration of the salts can be done if necessary) was added directly to the amine solution for the subsequent diazotransfer reaction.

General procedure for the reaction of triflic azide with amines. For organic soluble substrates, 1.0 g of substrate was dissolved in 5 mL of acetonitrile (pyridine). In case of saline substrates, water was employed. $CuSO_4$ (1 mole %) and NEt_3 (2 equilalents per substrate amine) were added to the solution while stirring. The mixture was cooled in an ice bath, followed the by the dropwise addition of an acetonitrile solution of triflyl azide (1.2 equiv per amino group, based on the amount of triflic anhydride used in the preparation of TfN_3). The reaction mixture was allowed to warm to room temperature. A homogeneous solution could be obtained after the addition of triflyl azide, and the reaction normally is completed within 12 h. The reaction was monitored by TLC. After its completion the solvent was removed by rotary evaporation and the crude product was purified using silica gel chromatography. The purification proved to be difficult, mainly due to the co-elution of a by-product derived from triflic anhydride. Multiple purifications by column chromatography were performed in some instances.

(1*R*,2*R*)-2-azido-1-(4-nitrophenyl)propane-1,3-diol (149).

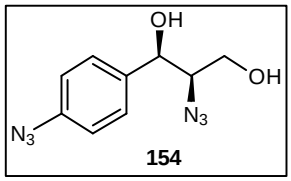


149

Oil. IR ($CHCl_3$): ν 3369, 2109, 1604, 1518, 1349, 1194, 1082, 857, 772, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* =

8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 5.04 (d, *J* = 4.4 Hz, 1H), 3.59 (dd, *J* = 11.6, 4.0 Hz, 1H), 3.71 – 3.67 (m, 1H), 3.44 (dd, *J* = 9.2, 5.2 Hz, 1H), 2.65 (s, 1H), 2.15 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.55, 127.36, 123.83, 106.44, 73.73, 67.91, 62.76. HRESI+MS: ($C_9H_{10}N_4O_4Na$) Calc: 261.0600. Found: 261.0587.

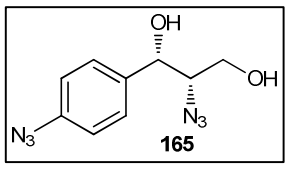
(1*R*,2*R*)-2-azido-1-(4-azidophenyl)propane-1,3-diol (154).



154

Oil. $[\alpha]^{25}_D$ -90.00 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 4.73 (d, *J* = 6.0 Hz, 1H), 3.59 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.44 (dd, *J* = 11.0, 7.0 Hz, 1H), 2.65 (s, 1H), 2.15 (s, 1H). ^{13}C NMR (100 MHz, MeOD) δ 140.93, 140.05, 129.30, 119.93, 74.15, 70.80, 62.95. HRESI-MS: ($C_9H_{10}N_6O_2Na$) Calc: 257.0763. Found: 257.0769.

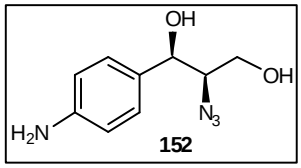
(1*S*,2*S*)-2-azido-1-(4-azidophenyl)propane-1,3-diol (165).



165

Oil. $[\alpha]^{25}_D$ +87.00 (c = 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, MeOD) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 4.73 (d, *J* = 6.0 Hz, 1H), 3.59 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.44 (dd, *J* = 11.0, 7.0 Hz, 1H), 2.65 (s, 1H), 2.15 (s, 1H). ^{13}C NMR (100 MHz, MeOD) δ 140.93, 140.05, 129.30, 119.93, 74.15, 70.80, 62.95.

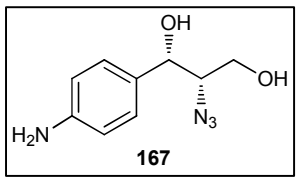
(1*R*,2*R*)-1-(4-aminophenyl)-2-azidopropane-1,3-diol (152).



152

Oil. $[\alpha]^{25}_{D}$ -66.00 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.84 (s, 1H), 4.53 (d, *J* = 7.2 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 1H), 3.76 (s, 2H), 3.74 – 3.41 (m, H), 3.41 – 3.18 (m, 23H), 2.02 (s, 21H), 1.24 (t, *J* = 7.1 Hz, 22H). ^{13}C NMR (101 MHz, MeOD) δ 148.62, 132.02, 128.57, 116.40, 74.90, 71.30, 63.11. HRMS: ($C_9H_{13}N_4O_2$) Calc: 209.1039. Found: 209.1039.

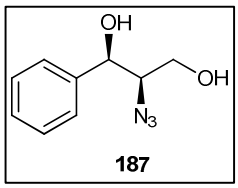
(1*S*,2*S*)-1-(4-aminophenyl)-2-azidopropane-1,3-diol (167).



167

Oil. $[\alpha]^{25}_{D}$ +68.60 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 7.13 (d, *J* = 8.3 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.53 (d, *J* = 7.2 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 1H), 3.58 – 3.44 (m, 2H), 3.43 – 3.27 (m, 2H), 2.02 (s, 2H), 1.24 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, MeOD) δ 148.60, 132.04, 128.57, 116.41, 74.90, 71.30, 63.11. HRMS: ($C_9H_{12}N_4O_2Na$) Calc: 231.0858. Found: 231.0853.

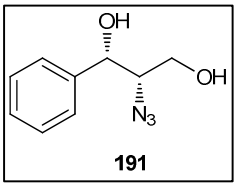
(1*R*,2*R*)-2-azido-1-phenylpropane-1,3-diol (187). Colorless oil.



187

$[\alpha]^{25}_{D}$ -80.40 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 7.40 (ddd, *J* = 14.5, 7.9, 4.2 Hz, 4H), 7.35 – 7.28 (m, 1H), 4.74 (d, *J* = 6.0 Hz, 1H), 3.64 – 3.54 (m, 2H), 3.48 (ddd, *J* = 20.8, 13.2, 7.7 Hz, 1H), 3.33 (s, 1H), 1.20 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, MeOD) δ 142.95, 129.42, 128.92, 127.66, 74.80, 70.97, 63.01.

(1*S*,2*S*)-2-azido-1-phenylpropane-1,3-diol (191). Oil. $[\alpha]^{25}_{D}$ +76.60 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 7.49 – 7.35 (m, 4H), 7.31 (t, *J* = 7.0 Hz, 1H), 4.74 (d, *J* = 6.0 Hz, 1H), 3.58 (dt, *J* = 6.7, 3.6 Hz, 2H), 3.48 (ddd, *J* = 20.7, 13.2, 7.7 Hz, 1H), 3.33 (s, 1H). ^{13}C NMR (101 MHz, MeOD) δ 142.96, 129.42, 128.92, 127.67, 74.81, 70.98, 63.02.



191

General procedure for modified Sandmeyer (bromination) reaction.

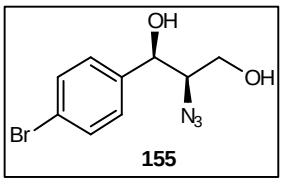
To a solution of aminoarene (5.0 mmol) in a mixture of 25 mL of DMSO and KNO_2 (1.70 g, 20 mmol) was added dropwise a solution of 47% HBr (2.49 mL, 20 mmol) and KI (4.15 g, 25 mmol) dissolved in DMSO (25 mL) at 35 °C. When the addition was complete, the mixture was further stirred for an additional 10 min at 35 °C and then transferred to a solution containing K_2CO_3 (5 g) in 100 mL ice water. The reaction mixture was added to a volume of diethyl ether, and the ethereal extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded the crude product.

General procedure for Sandmeyer (bromination) reaction.

An aqueous solution of $NaNO_2$ (1.27 g, 18.85 mmol, 50 ml H_2O) was added dropwise to a solution of aminoarene (3.76 g, 16.8 mmol) in 35 ml of 48% aqueous HBr at 0 ^{o}C. After addition was complete, the mixture was stirred for 30 min at 0 ^{0}C. The mixture was then added dropwise to a solution of CuBr (2.65g, 18.45 mmol) in 15 ml 48% aqueous HBr. The mixture was warmed to room temperature and stirred for additional 16 hours. The reaction mixture was neutralized with 3 M aqueous NaOH, filtered through a pad of

Celite, and extracted with EtOAc (3 x 100 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated to give 1.2 g (4.17 mmol) of crude product.

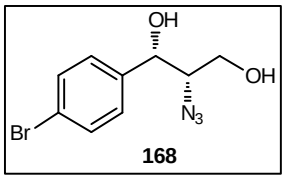
(1*R*,2*R*)-2-azido-1-(4-bromophenyl)propane-1,3-diol (155).



155

Oil. $[\alpha]^{25}_D$ -74.50 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone) δ 7.58 – 7.51 (m), 7.42 (d, *J* = 8.4 Hz), 4.92 (d, *J* = 4.4 Hz), 4.24 (s), 3.75 (dd, *J* = 10.7, 3.3 Hz), 3.62 (d, *J* = 6.8 Hz), 3.57 (dd, *J* = 7.9, 3.2 Hz), 3.06 (s), 2.57 (s). ^{13}C NMR (100 MHz, d_6-acetone) δ 141.84, 131.11, 128.65, 120.81, 72.69, 69.00, 61.82. HRESI+MS: ($C_9H_{10}BrN_3O_2Na$) Calc: 293.9854. Found: 293.9860.

(1*R*,2*R*)-2-azido-1-(4-bromophenyl)propane-1,3-diol (168).



168

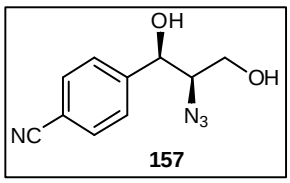
Oil. $[\alpha]^{25}_D$ +78.00 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone) δ 7.58 – 7.51 (m), 7.42 (d, *J* = 8.4 Hz), 4.92 (d, *J* = 4.4 Hz), 4.24 (s), 3.75 (dd, *J* = 10.7, 3.3 Hz), 3.62 (d, *J* = 6.8 Hz), 3.57 (dd, *J* = 7.9, 3.2 Hz), 3.06 (s), 2.57 (s). ^{13}C NMR (100 MHz, d_6-acetone) δ 141.84, 131.11, 128.65, 120.81, 72.69, 69.00, 61.82.

General procedure for Sandmeyer (cyanation) reaction.

To the aminoarene (10.26 g, 49 mmol) was added concentrated HCl (26 mL) and H_2O (130 mL) at room temperature, and then cooled to 0^{o}C. The resulting suspension was diazotized at 0 to 5 ^{o}C with $NaNO_2$ (3.7 g, 53 mmol) in H_2O (20 mL). After stirring for 30 minutes at 0 ^{o}C, the mixture was added to a solution of CuCN (9.23 g, 0.085 mol) and KCN (16.6g, 0.255 mol) in H_2O (80 mL). The mixture was vigorously stirred at 0 ^{o}C for

1 hour and then warmed to 50 ^{o}C. After cooling, the mixture was extracted with EtOAc. The organic phase was washed with 1 M NaOH (90 mL), H_2O (90 mL), dried over Na_2SO_4 and evaporated. Silica gel column chromatography (EtOAc:hexanes 1:1) yielded the nitrile product.

4-((1*R*,2*R*)-2-azido-1,3-dihydroxypropyl)benzonitrile (157).



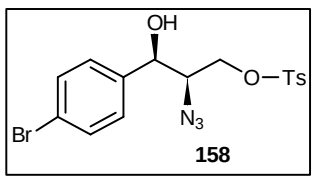
157

Oil. $[\alpha]^{25}_{D}$ -39.59 (c =0.5, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone) δ 7.78 (d, *J* = 8.3 Hz), 7.68 (d, *J* = 8.2 Hz), 5.13 (d, *J* = 4.7 Hz), 3.85 – 3.78 (m), 3.63 (ddt, *J* = 11.0, 6.7, 5.5 Hz), 3.13 (s). ^{13}C NMR (100 MHz, d_6-acetone) δ 147.97, 131.93, 127.52, 118.50, 111.13, 72.72, 68.59, 61.81.

General Experimental Procedure for the Tosylation of 1,3-diols.

To a solution of diol (10 mmol) in DCM (20 mL) was added Bu_2SnO (0.2 mmol), p-TsCl (10 mmol), and Et_3N (10 mmol). The reaction mixture was stirred until TLC indicated complete consumption of the starting material (8-12 hours). The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was crystallized or purified using silica gel chromatography to afford the desired monotosylate.

(2*R*,3*R*)-2-azido-3-(4-bromophenyl)-3 hydroxypropyl 4-methylbenzenesulfonate (158).

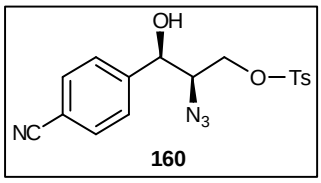


158

Oil. $[\alpha]^{25}_{D}$ -35.80 (c =1,

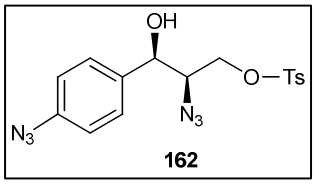
$CHCl_3$); ^1H NMR (400 MHz, d_6-acetone) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.49 (dd, *J* = 8.1, 5.3 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.34 (dd, *J* = 8.4, 4.3 Hz, 1H), 5.20 (dd, *J* = 4.6, 3.1 Hz, 1H), 4.91 (dd, *J* = 10.9, 5.5 Hz, 1H), 4.17 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.89 – 3.82 (m, 1H), 3.40 (q, *J* = 7.0 Hz, 1H), 2.91 (s, 2H), 2.88 (s, 1H), 2.47 (s, 2H).

(2*R*,3*R*)-2-azido-3-(4-cyanophenyl)-3-hydroxypropyl 4-methylbenzenesulfonate (160). Oil. ^1H NMR (400 MHz, d_6-acetone) δ 7.82 (d, *J* = 8.2 Hz), 7.72 (d, *J* = 8.2 Hz), 7.63 (d, *J* = 8.2 Hz), 7.47 (d, *J* = 8.1 Hz), 5.32 (d, *J* = 4.8 Hz), 4.30 (dd, *J* = 10.5, 3.5 Hz), 4.07 (dd, *J* = 10.4, 7.5 Hz), 3.99 – 3.93 (m), 2.46 (s). ^{13}C NMR (101 MHz, d_6-acetone) 146.54, 145.51, 132.61, 132.18, 130.17, 127.95, 127.51, 118.50, 111.57, 72.50, 69.30, 65.34, 20.89.



160

(2*R*,3*R*)-2-azido-3-(4-azidophenyl)-3-hydroxypropyl 4-methylbenzenesulfonate (162). Oil. $[\alpha]^{25}_D$ -60.59 (c =1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 4.75 (d, *J* = 5.6 Hz, 1H), 4.16 – 4.09 (m, 1H), 3.91 (dd, *J* = 10.5, 6.7 Hz, 1H), 3.72 (td, *J* = 6.3, 4.4 Hz, 1H), 2.65 (s, 1H), 2.46 (s, 2H), 2.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.51, 140.55, 136.07, 132.35, 130.12, 128.09, 127.91, 119.47, 72.83, 68.64, 65.74, 21.79.



162

Attempted Synthesis of 152 by Selective Reduction of Nitro Aromatic 149

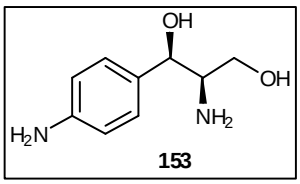
Method 1. The nitro derivative **149** (200 mg) was dissolved in THF (10 mL) and water (4 mL) was added. To this stirring mixture was added sodium dithionite (310 mg), and this was stirred at room temperature for 2 h. The solution was warmed to 40^{o}C for 10 min and then allowed to cool to room temperature. Another portion of sodium dithionite (150 mg) was added and stirring was continued for another 3 h. The reaction was monitored by TLC (acetone: chloroform; 1:1). After the reaction was complete, the solvent was evaporated and the residue purified by silica gel column chromatography. The product was isolated but contained significant contaminants.

Method 2. An aqueous solution (20 ml) containing K_2CO_3 (4.15 g, 30 mL) and $Na_2S_2O_4$ (4.70 g, 27 mmol) was added dropwise to a mixture of nitroarene **149** (6 mmol) and viologen (0.162 g, 0.3 mmol) in DCM (40 mL) and water (5 mL) under an inert atmosphere of argon. Stirring was continued for 2-8 h at 35^{o}C and then the aqueous layer was extracted with DCM (3 X 20 mL). The combined organic layers were dried, and treated with silica gel to remove any remaining viologen species. TLC analysis showed the same profile when compared to the reaction performed with $Na_2S_2O_4$.

Method 3. The nitro derivative **149** (238 mg, 1mmol) was treated with 606 mg of Na_2S in absolute EtOH. The reaction was monitored by TLC and presented the same profile on the other two previous methodologies, but appeared to contain less side products.

(1*R*,2*S*)-2-amino-1-(4-aminophenyl)propane-1,3-diol (153).

A 2 l round bottom flask was charged with 47.86 g of compound



153

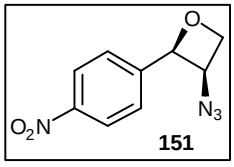
148, absolute ethanol and 7.17 g of Pd/C. After stirring for 5 minutes, vacuum was applied to the round bottom flask and a volume of hydrogen gas was introduced. The reaction was stirred at room temperature and monitored with TLC. The reduction was complete after 4 days. The reaction was filtered and the Pd/C recovered. The ethanol was evaporated and the residue recrystallized from ethanol to afford **153** in 90% yield.

Procedures for the synthesis of oxetanes.

Method 1. (K-*tert*-butoxide). 3.21g of tosylated precursor was dissolved in anhydrous THF (75 mL) and anhydrous benzene (75 mL). Potassium *tert*-butoxide (1.26 g) was added, and the mixture brought to reflux. Complete consumption of starting material was evident after an excess of base was added (1.5 additional equivalents). After cooling to room temperature, the reaction mixture was quenched with water and extracted with EtOAc, dried over sodium sulfate and evaporated. The crude residue was purified by silica gel chromatography [hexane:EtOAc gradient (100:0 to 60:40)] and homogenous product bands characterized.

Method 2 (Potassium carbonate) To a solution of tosylated precursor (130 mg) in MeOH (20 mL) was added K_2CO_3 (52 mg) at 0 °C and allowed to warm to room temperature. This stirred for 5 days with TLC monitoring. After completion, the methanol was removed under reduced pressure and the residue was purified using silica gel column chromatography. Yield of oxetane products ranged from 70-90%.

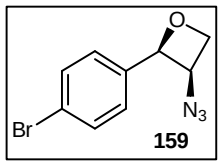
(2*R*,3*R*)-3-azido-2-(4-nitrophenyl)oxetane (151). Oil. $[\alpha]^{25}_{D}$ - 68.38 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone) δ 8.25 (d, *J* =



151

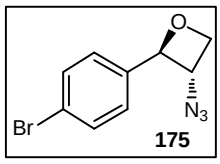
9.0 Hz, 2H), 7.75 (d, *J* = 9.0 Hz, 1H), 5.49 (d, *J* = 4.7 Hz, 1H), 5.13 (t, *J* = 4.6 Hz, 1H), 3.83 (m, 1H), 3.63 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.46 (dd, *J* = 13.0, 7.9 Hz, 1H). ^{13}C NMR (100 MHz, d_6-acetone) δ 150.15, 128.62, 124.18, 100.88, 73.99, 67.35, 52.40.

(2*R*,3*R*)-3-azido-2-(4-bromophenyl)oxetane (159). Oil. $[\alpha]^{25}_D$ -23.10 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 5.90 (d, *J* = 6.6 Hz, 1H), 4.99 (t, *J* = 7.0 Hz, 1H), 4.77 (dd, *J* = 12.1, 6.2 Hz, 1H), 4.60 – 4.52 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.80, 131.64, 128.03, 122.56, 86.07, 74.10, 57.97.



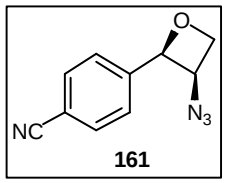
159

(2*R*,3*S*)-3-azido-2-(4-bromophenyl)oxetane (175). Oil. $[\alpha]^{25}_D$ +13.79 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 5.57 (d, *J* = 6.0 Hz, 1H), 4.76 (t, *J* = 7.1 Hz, 1H), 4.63 (t, *J* = 6.8 Hz, 1H), 4.28 (dd, *J* = 13.5, 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.63, 131.95, 126.95, 122.66, 88.04, 72.72, 61.56.



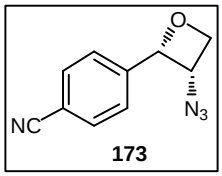
175

4-((2*R*,3*R*)-3-azidooxetan-2-yl)benzonitrile (161). Oil. $[\alpha]^{25}_D$ -24.10 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone) δ 7.84 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 6.11 (d, *J* = 6.7 Hz, 1H), 5.10 (dd, *J* = 11.7, 6.7 Hz, 1H), 5.02 (t, *J* = 7.0 Hz, 1H), 4.50 (dd, *J* = 6.6, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, d_6-acetone) δ 148.64, 147.60, 132.83, 128.34, 119.27, 112.08, 100.15, 73.90.



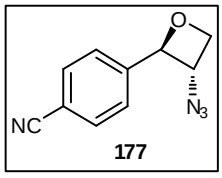
161

4-((2*S*,3*S*)-3-azidooxetan-2-yl)benzonitrile (173). Oil. $[\alpha]^{25}_{D}$ +25.20 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone) δ 7.84 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 6.11 (d, *J* = 6.7 Hz, 1H), 5.10 (dd, *J* = 11.7, 6.7 Hz, 1H), 5.02 (t, *J* = 7.0 Hz, 1H), 4.50 (dd, *J* = 6.6, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, d_6-acetone) δ 148.64, 147.60, 132.83, 128.34, 119.27, 112.08, 100.15, 73.90.



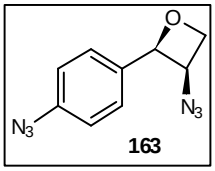
173

4-((2*R*,3*S*)-3-azidooxetan-2-yl)benzonitrile (177). Oil. $[\alpha]^{25}_{D}$ +19.80 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 5.70 (d, *J* = 5.5 Hz, 1H), 4.90 – 4.82 (m, 1H), 4.65 – 4.57 (m, 2H). ^{13}C NMR (101 MHz, d_6-acetone) δ 148.64, 147.60, 132.83, 128.34, 119.27, 112.08, 100.15, 73.90.



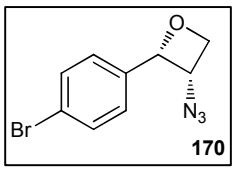
177

(2*R*,3*R*)-3-azido-2-(4-azidophenyl)oxetane (163). Oil. $[\alpha]^{25}_{D}$ -30.39 (c =1, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.91 (d, *J* = 6.6 Hz, 1H), 4.96 (t, *J* = 7.0 Hz, 1H), 4.75 (dd, *J* = 11.9, 6.5 Hz, 1H), 4.53 (dd, *J* = 7.1, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.17, 133.41, 127.92, 118.98, 86.07, 73.88, 58.11.



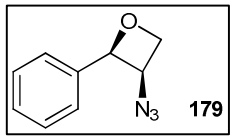
163

(2*S*,3*S*)-3-azido-2-(4-bromophenyl)oxetane (170). Oil. $[\alpha]^{25}_{D}$ +22.00 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 5.90 (d, *J* = 6.6 Hz, 1H), 4.99 (t, *J* = 7.0 Hz, 1H), 4.77 (dd, *J* = 12.1, 6.2 Hz, 1H), 4.60 – 4.52 (m, 1H).

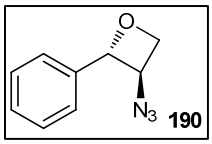


170

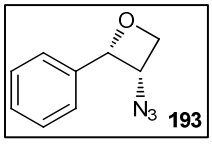
(2*R*,3*R*)-3-azido-2-phenyloxetane (179). Oil. $[\alpha]^{25}_{D}$ -38.40 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.35 (m, 3H), 5.97 (d, *J* = 6.7 Hz, 1H), 5.00 (t, *J* = 7.0 Hz, 1H), 4.78 (dd, *J* = 11.9, 6.7 Hz, 1H), 4.59 (dd, *J* = 6.9, 5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.74, 128.50, 128.45, 126.31, 86.65, 73.96, 58.04.



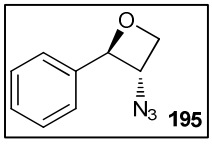
(2*S*,3*R*)-3-azido-2-phenyloxetane (190). Oil. $[\alpha]^{25}_{D}$ 7.2 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone)) δ 7.50 (dd, *J* = 8.0, 1.1 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.37 (ddd, *J* = 8.2, 2.6, 1.3 Hz, 1H), 5.59 (d, *J* = 5.7 Hz, 1H), 4.79 (t, *J* = 6.6 Hz, 1H), 4.64 – 4.46 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 139.76, 128.46 (x2C), 125.30, 88.81, 72.41, 61.46.



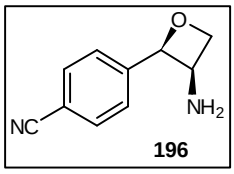
(2*S*,3*S*)-3-azido-2-phenyloxetane (193). Oil. $[\alpha]^{25}_{D}$ +51.20 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone)) δ 7.62 – 7.26 (m, 6H), 6.02 (d, *J* = 5.9 Hz, 1H), 5.08 – 4.89 (m, 2H), 4.58 – 4.40 (m, 1H). ^{13}C NMR (100 MHz, d_6-acetone)) δ 138.76, 129.06, 128.94, 127.31, 87.12, 74.30, 59.38.



(2*R*,3*S*)-3-azido-2-phenyloxetane (195). Oil. $[\alpha]^{25}_{D}$ -6.4 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone)) δ 7.49 (dd, *J* = 8.0, 1.1 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.36 (ddd, *J* = 8.2, 2.6, 1.3 Hz, 1H), 5.58 (d, *J* = 5.7 Hz, 1H), 4.86 – 4.73 (m, 1H), 4.62 – 4.46 (m, 2H). ^{13}C NMR (100 MHz, d_6-acetone)) δ 141.11, 129.45, 129.34, 126.41, 89.08, 73.08, 62.28.



4-((2*R*,3*R*)-3-aminooxetan-2-yl)benzonitrile (196). Oil. ^{1}H NMR (400 MHz, MeOD) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 3H), 5.94 (d, *J* = 6.8 Hz, 1H), 5.08 – 4.97 (m, 1H), 4.46 – 4.34 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 145.14, 133.38, 128.12, 119.76, 112.43, 89.15, 79.63, 51.66.



196

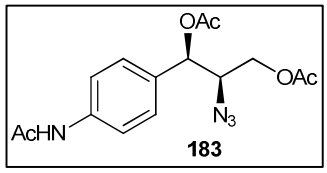
Attempted Grignard reactions of 159 with magnesium. A solution of (2*R*,3*R*)-3-azido-2-(4-bromophenyl)oxetane **159** (50 mg, 0.197 mmol) in anhydrous THF (10 mL) was added dropwise to magnesium turnings (5.91 mg) in anhydrous THF (20 mL) under an atmosphere of argon. A crystal of iodine was necessary to initiate the Grignard reaction. The reaction was refluxed for 2 h. The solvent was removed from the reaction mixture by rotary evaporation, and a solution of **161** (30 mg, 0.150 mmol) in anhydrous toluene (30 mL) was added slowly. The reaction mixture was refluxed for 12 h. An aliquot was taken from the reaction medium and quenched with NH_4Cl, to observe the formation of (2*R*,3*R*)-3-azido-2-phenyloxetane (**178**) by LC-MS. Only starting material remained.

Attempted Grignard reactions of 159 with iPrMgCl-LiCl.

Preparation of the reagent *i*-PrMgCl·LiCl: Magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol) were placed in an Ar-flushed flask, and anhydrous THF (50 mL) was added. A solution of iPrCl (100 mmol) in THF (50 mL) was slowly added at room temperature. The reaction started within a few minutes. After the addition, the

reaction mixture was stirred for 12 h at room temperature. The gray solution of iPrMgCl·LiCl was cannulated into another Ar-filled flask leaving behind excess Mg metal. Reaction with arylbromide **159**. A flame-dried argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of **159** (50 mg) in anhydrous THF (0.2 mL). *i*-PrMgCl.LiCl (2.0 M/THF, 0.2 mmol, 1.1 equiv) was added slowly at -40 °C, and the resulting mixture was stirred at this temperature for 12 h to complete the bromine-magnesium exchange (checked by reaction of aliquots with NH_4Cl). Nitrile **161** (50 mg in 2 mL of THF, 1.1 equiv) was added. The mixture was warmed to room temperature and stirred for 12 hours. This was quenched with saturated aqueous NH_4Cl. Although the Mg insertion was confirmed, no product was observed with the addition of the benzonitrile.

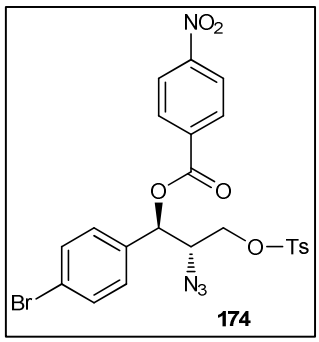
(1*R*,2*R*)-1-(4-acetamidophenyl)-2-azidopropane-1,3-diyl diacetate (182). Oil. ^{1}H NMR (400 MHz, MeOD) δ 7.59 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 5.81 (d, *J* = 7.3 Hz, 1H), 4.10 (dq, *J* = 5.4, 3.7 Hz, 1H), 3.84 (td, *J* = 7.5, 1.9 Hz, 1H), 2.12 (s, 1H), 2.10 (s, 2H), 2.04 (s, 1H). ^{13}C NMR (100 MHz, MeOD) δ 170.59, 170.32, 169.89, 139.13, 131.97, 127.38, 119.77, 74.98, 63.57, 62.89, 22.48, 19.47, 19.11.



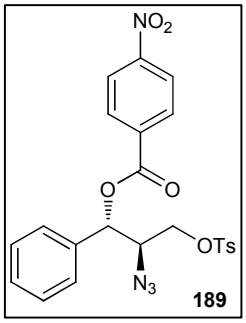
183

General Methodology for Misunobu Reactions. Diisopropylazodicarboxylate (DIAD) (0.07 mL, 0.45 mmol) was added to a solution of Ph_3P (75 mg, 0.45 mmol) in anhydrous THF (5 mL) at 0^{o}C under an inert atmosphere of argon. The solution was stirred for 15 minutes. A solution of the tosylated alcohol in THF (5 mL) was added dropwise. The

resulting bright yellow solution was stirred for 15 min at 0 °C and then 4 h at room temperature. The reaction was monitored by TLC. The solvent was removed, and the residue purified by silica gel column chromatography with hexanes:EtOAc (97:3).

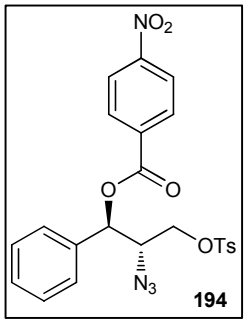


(1*R*,2*S*)-2-azido-1-(4-bromophenyl)-3-(tosyloxy)propyl 4-nitrobenzoate (174). $[\alpha]^{25}_{D}$ 5.0 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-acetone) δ 8.45 – 8.34 (m, 4H), 8.30 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.67 – 7.56 (m, 4H), 7.56 – 7.46 (m, 3H), 7.42 (d, *J* = 8.1 Hz, 2H), 6.11 (d, *J* = 6.7 Hz, 1H), 4.61 – 4.49 (m, 2H), 4.45 – 4.34 (m, 2H), 4.33 – 4.21 (m, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, d_6-acetone) δ 162.86, 151.09, 145.41, 135.36, 134.70, 131.75, 131.00, 130.04, 129.48, 129.42, 127.85, 123.70 , 122.61, 74.50, 68.10, 62.91, 20.58.



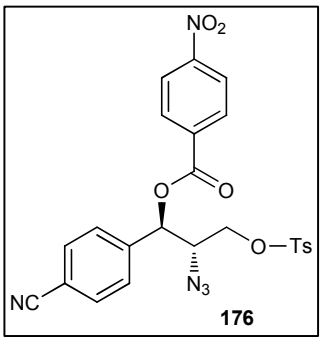
(1*S*,2*R*)-2-azido-1-phenyl-3-(tosyloxy)propyl 4-nitrobenzoate (189). $[\alpha]^{25}_{D}$ -9.57 (c = 1.0, $CHCl_3$) IR ($CHCl_3$,) ν 2117, 1734, 1600, 1530, 1267, 1178, 1099. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 28.9, 8.9 Hz, 4H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.36 (ddd, *J* = 24.5, 13.7, 5.8 Hz, 8H), 6.08 (d, *J* = 6.0 Hz, 1H), 4.23 (td, *J* = 6.3, 4.4 Hz, 1H), 4.17 (dd, *J* = 10.5, 4.3 Hz, 1H), 4.15 – 4.08 (m, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.08, 150.78, 145.50, 134.82, 132.14, 130.95, 130.05, 129.41, 128.94, 127.98, 127.18, 126.49, 123.63, 75.57, 67.63, 63.11, 21.02.

(1*R*,2*S*)-2-azido-1-phenyl-3-(tosyloxy)propyl 4-nitrobenzoate (194). $[\alpha]^{25}_{D}$ +12.65 (c = 1.0, $CHCl_3$) IR ($CHCl_3$,) ν 2117, 1734, 1600, 1530, 1267, 1178, 1099. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 28.9, 8.9 Hz, 4H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.36 (ddd, *J* = 24.5, 13.7, 5.8 Hz, 8H), 6.08 (d, *J* = 6.0 Hz, 1H), 4.23 (td, *J* = 6.3, 4.4 Hz, 1H), 4.17 (dd, *J* = 10.5, 4.3 Hz, 1H), 4.15 – 4.08 (m, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.08, 150.8, 145.50, 134.82, 132.14, 130.95, 130.05, 129.41, 128.94, 127.98, 127.18, 126.49, 123.63, 75.57, 67.63, 63.11, 21.02.



194

(1*R*,2*S*)-2-azido-1-(4-cyanophenyl)-3-(tosyloxy)propyl 4-nitrobenzoate (176). $[\alpha]^{25}_{D}$ +34.59 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, , d_6-acetone) δ 8.35 (dd, *J* = 20.3, 9.0 Hz, 4H), 7.80 (dd, *J* = 14.4, 8.2 Hz, 6H), 7.42 (d, *J* = 8.0 Hz, 2H), 6.20 (d, *J* = 6.7 Hz, 1H), 4.61 (td, *J* = 6.5, 3.5 Hz, 1H), 4.42 (dd, *J* = 10.9, 3.5 Hz, 1H), 4.31 (dd, *J* = 10.9, 6.3 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, Acetone) δ 162.90, 159.52, 156.35, 156.31, 145.47, 141.17, 134.45, 132.56, 131.07, 130.07, 128.37, 127.86, 123.67, 112.80, 74.46, 68.31, 62.82, 21.34.



176

CHAPTER 5: BIBLIOGRAPHY

Abe, M., T. Minamoto, et al. (2002). Reaction of 7,7-diphenyl-6-oxabicyclo[3.2.0]hept-1-ene with ROH; controlling factors on the regioselectivity in the nucleophilic addition reaction." Tetrahedron **58** (35): 7043-7047.

Akazome, M., Y. Tsuji, et al. (1990). "Ruthenium complex-catalyzed selective deoxygenation of ketoximes to ketimines." Chem. Lett. **4**.

Albert, S., S. Robin, et al. (2001). "Preparation of oxetanes by 4-endo trig electrophilic cyclisations of cinnamic alcohols." Tetrahedron Lett. **42**(13): 2477-2479.

Alonso, F. F., L. R.; Fanwick, P. E.; Lorenzo, E.; Yus, M. (2000). "Synthesis of substituted 1,6-dioxaspiro[3.4]octanes from 3-chloro-2-(chloromethyl)prop-1-ene." Synthesis (7): 949-952.

Alper, P. B., S.-C. Hung, et al. (1996). "Metal catalyzed diazo transfer for the synthesis of azides from amines." Tetrahedron Lett. **37**(34): 6029-6032.

Ameijde, J. V and R. M. J. Liskamp (2003). "Synthesis of novel trivalent amino acid glycoconjugates based on the cyclotriveratrylene ('CTV') scaffold." Org. Biomol. Chem. **1**(15): 2661-2669.

Anderson, B. G., W. E. Bauta, et al. (2008). "Isolation, Synthesis, and Characterization of Impurities and Degradants from the Clofarabine Process." Org. Process Res. Dev. **12**(6): 1229-1237.

Ansaldi, M., D. Marolt, et al. (2002). "Specific activation of the Bacillus quorum-sensing systems by isoprenylated pheromone variants." Mol. Microbiol. **44**(6): 1561-1573.

Arjona, O., R. F. de la Pradilla, et al. (1987). "Regio- and stereoselective electrophilic additions to and -2-hydroxy-2-methyl-7-oxabicyclo[2.2.1]hept-5-ene." Tetrahedron Lett. **28**(45): 5549-5550.

Arjona, O., R. F. de la Pradilla, et al. (1989). "Regioselective electrophilic additions to 2-oxygenated-7-oxabicyclo[2.2.1]Hept-5-enes: A simple entry into the 4,7-dioxatricyclo[3.2.1.03,6]octaneskeleton." Tetrahedron **45**(14): 4565-4578.

Arjona, O., R. Fernandez de la Pradilla, et al. (1992). "Temperature-controlled synthesis of 4,7-dioxatricyclo[3.2.1.03,6]octane derivatives." J. Org. Chem. **57**(2): 772-774.

Atkinson, S., J. P. Throup, et al. (1999). "A hierarchical quorum-sensing system in Yersinia pseudotuberculosis is involved in the regulation of motility and clumping." Mol. Microbiol. **33**(6): 1267-1277.

Bach, T. and J. Schroder (1999). "Photocycloaddition of N-acyl enamines to aldehydes and its application to the synthesis of diastereomerically pure 1,2-amino alcohols." J. Org. Chem. **64**(4): 1265-1273.

Bach, T. and J. Schröder (1997). "Synthesis of syn- and anti-1,2-amino alcohols by regioselective ring opening reactions of cis-3-aminooxetanes." Tetrahedron Lett. **38**(21): 3707-3710.

Baik, W., W. Luan, et al. (2005). "Efficient one-pot transformation of aminoarenes to haloarenes using halodimethylisulfonium halides generated in situ." Can. J. Chem. **83**(3): 213-219.

Barks, J. M., D. W. Knight, et al. (1994). "Predictive models for the overall 5-endo-trig iodocyclisation of homoallylic alcohols." Tetrahedron Lett. **35**(39): 7259-7262.

Bassler, B. L. and R. Losick (2006). "Bacterially Speaking." Cell **125**(2): 237-246.

Behrens, C. H. S., K. S.; (1983). "New transformations of 2,3-epoxy alcohols and related derivatives. Easy routes to homochiral substances." Aldrichimica Acta **16**(4): 64-79.

Ben-Jacob, E. and H. Levine (2006). "Self-engineering capabilities of bacteria." J. Royal Soc. Interface **3**(6): 197-214.

Birman, V. B. and S. J. Danishefsky (2002). "The total synthesis of (±)-merrilactone A." J. Am. Chem. Soc. **124**(10): 2080-2081.

Boger, D. L., M. A. Patane, et al. (1994). "Total synthesis of bouvardin, O-methylbouvardin, and O-methyl-N9-desmethylbouvardin." J. Am. Chem. Soc. **116**(19): 8544-8556.

Boger, D. L. and D. Yohannes (1991). "Intramolecular Ullmann condensation reaction: an effective approach to macrocyclic diaryl ethers." J. Org. Chem. **56**(5): 1763-1767.

Bonini, C., C. Federici, et al. (1995). "C-1 Reactivity of 2,3-epoxy alcohols via oxirane opening with metal halides: Applications and synthesis of naturally occurring 2,3-octanediol, muricatacin, 3-octanol, and 4-dodecanolide." J. Org. Chem. **60**(15): 4803-4812.

Boojamra, C. G. C., L. S.; Hecker, S. J.; Glinka, T. W.; Shuster, D. E.; (2003). "Florfenicol-type antibiotics USA.", Schering-Plough Animal Health Corporation US 7,041,670 B2**:** 77.

Brennan, N. K., X. Guo, et al. (2004). "Second-generation, highly abbreviated route for elaboration of the oxetane D-ring in a fully functionalized taxane." J. Org. Chem. **70**(2): 732-734.

Brouillette, W. J., S. N. Bajpai, et al. (2003). "Pyrrolidinobenzoic acid inhibitors of influenza virus neuraminidase: modifications of essential pyrrolidinone ring substituents." Bioorg. Med. Chem. **11**(13): 2739-2749.

Brown, W. L. and A. G. Fallis (1985). "Epimerization of bicyclic vinyl -alcohols [2,3] sigmatropic rearrangement." Tetrahedron Lett. **26**(5): 607-610.

Bruckner, R. (2010). Organic Mechanisms: Reactions, Stereochemistry and Synthesis. Berlin Heidelberg, Springer-Verlag.

Bühler, S., I. Lagoja, et al. (2004). "New types of very efficient photolabile protecting groups based upon the [2-(2-nitrophenyl)propoxy]carbonyl (NPPOC) moiety." Helvetica Chimica Acta **87**(3): 620-659.

Burke, S. D. and E. A. Voight (2000). "Formal synthesis of (+)-3-deoxy-d-glycero-d-galacto-2-nonulosonic acid (KDN) via desymmetrization by ring-closing metathesis." Org. Lett. **3**(2): 237-240.

Burr, T., A. M. L. Barnard, et al. (2006). "Identification of the central quorum sensing regulator of virulence in the enteric phytopathogen, *Erwinia carotovora*: the VirR repressor." Mol. Microbiol. **59**(1): 113-125.

Cao, J. G. and E. A. Meighen (1989). "Purification and structural identification of an autoinducer for the luminescence system of *Vibrio harveyi*." J. Biol. Chem. **264**(36): 21670-21676.

Castang, S., S. Reverchon, et al. (2006). "Direct evidence for the modulation of the activity of the *Erwinia chrysanthemi* quorum-sensing regulator ExpR by acylhomoserine lactone pheromone." J. Biol. Chem. **281**(40): 29972-29987.

Cavender, C. J. and V. J. Shiner (1972). "Trifluoromethanesulfonyl azide. Its reaction with alkyl amines to form alkyl azides." J. Org. Chem. **37**(22): 3567-3569.

Chan, W. C., B. J. Coyle, et al. (2004). "Virulence regulation and quorum sensing in *Staphylococcal* infections: Competitive AgrC antagonists as quorum sensing inhibitors." J. Med. Chem. **47**(19): 4633-4641.

Chun, W., J. Cui, et al. (1997). "Purification, characterization and biological role of a pheromone produced by *Xanthomonas campestrispv.campestris*." Physiol. Mol. Plant Pathol. **51**(1): 1-14.

Cisar, E. A. G., E. Geisinger, et al. (2009). "Symmetric signalling within asymmetric dimers of the *Staphylococcus aureus* receptor histidine kinase AgrC." Mol. Microbiol. **74**(1): 44-57.

Clausen, R. P. and M. Bols (2000). "A method for syn-dihydroxylation of double bonds cis to a hydroxymethyl substituent." J. Org. Chem. **65**(9): 2797-2801.

Clayden, J., C. J. Menet, et al. (2002). "Synthesis of (-)-kainic acid using chiral lithium amides in an asymmetric dearomatizing cyclization." Tetrahedron **58**(23): 4727-4733.

Conrow, R. E. and W. D. Dean (2008). "Diazidomethane explosion." Org. Process Res. Dev. **12**(6): 1285-1286.

Couladouros, E. A. and I. C. Soufli (1995). "Total synthesis of natural (-)-combretastatin D-1." Tetrahedron Lett. **36**(51): 9369-9372.

Craig, D., V. R. N. Munasinghe, et al. (1999). "Template-directed intramolecular C-glycosidation. cation-mediated synthesis of ketooxetanes from thioglycosides." Tetrahedron **55**(52): 15025-15044.

de Kievit, T. R. a. I., B. H. (2000). "Bacterial quorum sensing in pathogenic relationships." Infect. Immun. **68**(9): 4839-4849.

de la Torre, M. C., A. Maggio, et al. (2000). "Hemisynthesis of oxetane-containing neoclerodane diterpenoids." Tetrahedron **56**(40): 8007-8017.

DeNinno, M. P., J. B. Etienne, et al. (1995). "A method for the selective reduction of carbohydrate 4,6-O-benzylidene acetals." Tetrahedron Lett. **36**(5): 669-672.

Denis, J. N., A. E. Greene, et al. (1986). "An efficient, enantioselective synthesis of the taxol side chain." J. Org. Chem. **51**(1): 46-50.

Dollinger, L. M., A. J. Ndakala, et al. (1999). "Preparation and properties of 2-methyleneoxetanes." J. Org. Chem. **64**(19): 7074-7080.

Dong, Y.-H., L.-H. Wang, et al. (2001). "Quenching quorum-sensing-dependent bacterial infection by an N-acyl homoserine lactonase." Nature **411**(6839): 813-817.

Dong, Y.-H., J.-L. Xu, et al. (2000). "AiiA, an enzyme that inactivates the acylhomoserine lactone quorum-sensing signal and attenuates the virulence of *Erwinia carotovora*." PNAS, USA **97**(7): 3526-3531.

Dufour, A., T. Hindré, et al. (2007). "The biology of lantibiotics from the lacticin 481 group is coming of age." FEMS Microbiol. Rev. **31**(2): 134-167.

Dunlap, P. V. (1999). "Quorum regulation ofluminescence in *Vibrio fischeri*." J. Molec. Microbiol. Biotechnol. **1**(1): 5-12.

Eberl, L., M. K. Wilnson, et al. (1996). "Involvement of N-acyl-L-homoserine lactone autoinducers in controlling the multicellular behaviour of *Serratia liquefaciens*." Mol. Microbiol. **20**(1): 127-136.

Ehlinger, E. and P. Magnus (1980). "Silicon in synthesis. 10. The (trimethylsilyl)allyl anion: A beta-acyl anion equivalent for the conversion of aldehydes and ketones into gamma-lactones." J. Am. Chem. Soc. **102**(15): 5004-5011.

Ehrlich, J., Q. R. Bartz, et al. (1947). "Chloromycetin, a new antibiotic from a soil actinomycete." Science **106**(2757): 417.

Enquist, P. A., P. Nilsson, et al. (2003). "Ultrafast chemistry: Cobalt carbonyl-mediated synthesis of diaryl ketones under microwave irradiation." Org. Lett. **5**(25): 4875-4878.

Evans, R. D. M., Joseph W.; Schauble, J. Herman (1988). "Halocyclization of unsaturated alcohols and carboxylic acids using bis(sym-collidine)iodine(I) perchlorate." Synthesis(11): 862-868.

Feldman, K. S., M. R. Iyer, et al. (2006). "Allenyl azide cycloaddition chemistry. Synthesis of annelated indoles from 2-(allenyl)phenyl azide substrates." Org. Lett. **8**(14): 3113-3116.

Fergus, S., S. J. Eustace, et al. (2004). "Nitrile ylide dimerization: Investigation of the carbene reactivity of nitrile ylides." J. Org. Chem. **69**(14): 4663-4669.

Fischer, W. and J. P. Anselme (1967). "Reaction of amine anions with p-toluenesulfonyl azide. Novel azide synthesis." J. Am. Chem. Soc. **89**(20): 5284-5285.

Forsyth, C. J., J. Xu, et al. (2006). "Antibodies with broad specificity to azaspiracids by use of synthetic haptens." J. Am. Chem. Soc. **128**(47): 15114-15116.

Fowler, S. A., D. M. Stacy, et al. (2008). "Design and synthesis of macrocyclic peptomers as mimics of a quorum sensing signal from *Staphylococcus aureus*." Org. Lett. **10**(12): 2329-2332.

Frezza, M., L. Soulere, et al. (2007). "Ac2-DPD, the bis-(O)-acetylated derivative of 4,5-dihydroxy-2,3-pentanedione (DPD) is a convenient stable precursor of bacterial quorum sensing autoinducer AI-2." Bioorg. Med. Chem. Lett. **17**(5): 1428-1431.

Fringuelli, F., F. Pizzo, et al. (2003). "First one-pot copper-catalyzed synthesis of α-hydroxy-β-amino acids in water. A new protocol for preparation of optically active norstatines." J. Org. Chem. **68**(18): 7041-7045.

Fringuelli, F., F. Pizzo, et al. (2001). "AlCl3 as an efficient Lewis acid catalyst in water." Tetrahedron Lett. **42**(6): 1131-1133.

Fuqua, C. and E. P. Greenberg (2002). "Signalling: Listening in on bacteria: acyl-homoserine lactone signalling." Nature Rev. Mol. Cell Biol. **3**(9): 685-695.

Galatsis, P., S. D. Millan, et al. (1997). "Enantioselective construction of cyclic ethers by an aldol-cyclization sequence." J. Org. Chem. **62**(15): 5048-5056.

Galatsis, P., S. D. Millan, et al. (1994). "Tandem aldol-cyclization sequence for the construction of cyclic ethers. The formation of substituted tetrahydrofurans." J. Org. Chem. **59**(22): 6643-6651.

Galatsis, P. and D. J. Parks (1994). "Stereoselective synthesis of substituted oxetanes." Tetrahedron Lett. **35**(36): 6611-6614.

George, E. A., R. P. Novick, et al. (2008). "Cyclic peptide inhibitors of *Staphylococcal* virulence prepared by Fmoc-based thiolactone peptide synthesis." J. Am. Chem. Soc. **130**(14): 4914-4924.

Geske, G. D., J. C. O'Neill, et al. (2007). "Modulation of bacterial quorum sensing with synthetic ligands: systematic evaluation of N-acylated homoserine lactones in multiple species and new insights into their mechanisms of action." J. Am. Chem. Soc. **129**(44): 13613-13625.

Gilson, L., A. Kuo, et al. (1995). "AinS and a new family of autoinducer synthesis proteins." J. Bacteriol. **177**(23): 6946-6951.

Goddard-Borger, E. D. and R. V. Stick (2007). "An efficient, inexpensive, and shelf-stable diazotransfer reagent: Imidazole-1-sulfonyl azide hydrochloride." Org. Lett. **9**(19): 3797-3800.

Gonzalez Barrios, A. F., R. Zuo, et al. (2006). "Autoinducer 2 controls biofilm Formation in *Escherichia coli* through a novel motility quorum-sensing regulator (MqsR, B3022)." J. Bacteriol. **188**(1): 305-316.

Grabley, S. T., R. (1999). Drug Discovery from Nature. Berlin Heidelberg New York, Springer Verlag.

Gray, K., J. Pearson, et al. (1996). "Cell-to-cell signaling in the symbiotic nitrogen-fixing bacterium Rhizobium leguminosarum: autoinduction of a stationary phase and rhizosphere-expressed genes." J. Bacteriol. **178**(2): 372-376.

Haddad, M. and M. Larchevêque (2001). "An alternative stereoselective synthesis of trans-(2R,3R)-3-hydroxypipecolic acid." Tetrahedron Lett. **42**(31): 5223-5225.

Hanessian, S., G. Huang, et al. (2005). "Total synthesis of N-malayamycin A and related bicyclic purine and pyrimidine nucleosides." J. Org. Chem. **70**(17): 6721-6734.

Hanson, R. M. (1991). "The synthetic methodology of nonracemic glycidol and related 2,3-epoxy alcohols." Chem. Rev. **91**(4): 437-475.

Hanzelka, B. L. G., E. P. (1995). "Evidence that the N-terminal region of the *Vibrio fischeri* LuxR protein constitutes an autoinducer-binding domain." J. Bacteriol. **177**(3): 815–817.

Hara, T., S. R. Durell, et al. (2006). "Probing the structural requirements of peptoids that inhibit HDM2−p53 interactions." J. Am. Chem. Soc. **128**(6): 1995-2004.

Harraghy, N., S. Kerdudou, et al. (2007). "Quorum-sensing systems in *Staphylococci* as therapeutic targets." Anal. Bioanal. Chem. **387**(2): 437-444.

He, W., J. Huang, et al. (2007). "Total synthesis of (±)-merrilactone A." J. Am. Chem. Soc. **130**(1): 300-308.

Hentzer, M., L. Eberl, et al. (2003). "Quorum sensing: A novel target for the treatment of biofilm infections." BioDrugs **17**(4): 241-250.

Hentzer, M. and M. Givskov (2003). "Pharmacological inhibition of quorum sensing for the treatment of chronic bacterial infections." J. Clin. Invest. **112**(9): 1300-1307.

Hentzer, M., K. Riedel, et al. (2002). "Inhibition of quorum sensing in *Pseudomonas aeruginosa* biofilm bacteria by a halogenated furanone compound." Microbiol. **148**(1): 87-102.

Hoang, T. T., S. A. Sullivan, et al. (2002). "{beta}-Ketoacyl acyl carrier protein reductase (FabG) activity of the fatty acid biosynthetic pathway is a determining factor of 3-oxo-homoserine lactone acyl chain lengths." Microbiol. **148**(12): 3849-3856.

Holden, M. T. G., S. Ram Chhabra, et al. (1999). "Quorum-sensing cross talk: isolation and chemical characterization of cyclic dipeptides from *Pseudomonas aeruginosa* and other Gram-negative bacteria." Mol. Microbiol. **33**(6): 1254-1266.

Holton, R. A., H. B. Kim, et al. (2002). "First total synthesis of taxol. 2. Completion of the C and D rings." J. Am. Chem. Soc. **116**(4): 1599-1600.

Homsi, F., S. Robin, et al. (2000). "Preparation of bis(2,4,6-trimethylpyridine)iodine(I) hexafluorophosphate and bis(2,4,6-trimethylpyridine) bromine(I) hexafluorophosphate." Org. Syn. **77**: 206-211.

Homsi, F. and G. Rousseau (1999). "4-Endo-trig cyclization Processes Using Bis(collidine)bromine(I) Hexafluorophosphate as Reagent: Preparation of 2-Oxetanones, 2-Azetidinones, and Oxetanes." J. Org. Chem. **64**(1): 81-85.

Huber, D., G. Andermann, et al. (1988). "Selective reduction of aromatic / aliphatic nitro groups by sodium sulfide." Tetrahedron Lett. **29**(6): 635-638.

Hullar, T. L. and S. B. Siskin (2002). "Facile bromination by N-bromosuccinimide of benzylidene acetals of carbohydrates. Application to the synthesis of 2,6-imino carbohydrates (substituted 2,5-oxazabicyclo[2.2.2] octanes)." J. Org. Chem. **35**(1): 225-228.

Imagawa, H. S., T.; Suzuki, T.; Takao, H.; Yamada, H.; Sugihara, T.; Nishizawa, M. (1998). "Intramolecular oxymercuration with mercuric triflate." Chem. Pharm. Bull. **46**(8): 1341-1342.

Inoue, M., N. Lee, et al. (2007). "Total synthesis and bioactivity of an unnatural enantiomer of merrilactone A: Development of an enantioselective desymmetrization strategy." J. Org. Chem. **72**(8): 3065-3075.

Inoue, M., T. Sato, et al. (2006). "Asymmetric total synthesis of (-)-merrilactone A: Use of a bulky protecting group as long-range stereocontrolling element." Angew. Chem. Int. Ed. **45**(29): 4843-4848.

Irie, T., M. Izawa, et al. (1968). "Laureatin, a constituent from yamada." Tetrahedron Lett. **9**(17): 2091-2096.

Irie, T., M. Izawa, et al. (1970). "Laureatin and isolaureatin, constituents of Laurencia nipponica Yamada." Tetrahedron **26**(3): 851-870.

Isaacs, R. C. A., M. J. Di Grandi, et al. (2002). "Synthesis of an enantiomerically pure intermediate containing the CD substructure of taxol." J. Org. Chem. **58**(15): 3938-3941.

Ishii, S. Y., T.; Ebihara, A.; Okamoto, A.; Manzoku, M.; Hayashi, H. (2010). "Crystal structure of the peptidase domain of *Streptococcus ComA*, a bifunctional ATP-binding cassette transporter involved in the quorum-sensing pathway." J. Biol. Chem. **285**(14): 10777-10785.

Islas-Gonzalez, G., J. Benet-Buchholz, et al. (2006). "Boron trifluoride-induced, new stereospecific rearrangements of chiral epoxy ethers. Ready access to enantiopure 4-(diarylmethyl)-1,3-dioxolanes and 4,5-disubstituted yetrahydrobenzo[c]oxepin-4-ols." J. Org. Chem. **71**(4): 1537-1544.

Ito, K. F., T.; Katsuki, T. (1997). "A New enantiospecific approach to the bislactone structure: Formal syntheses of (-)-avenaciolide and (-)-isoavenaciolide." Heterocycles **46**(1): 401-411

Jenkinson, S. F., T. Harris, et al. (2004). "Oxetane cis- and trans [beta]-amino-acid scaffolds from D-xylose by efficient SN2 reactions in oxetane rings: methyl and hydroxymethyl analogues of the antibiotic oxetin, an oxetane [beta]-amino-acid." Tetrahedron: Asymm. **15**(17): 2667-2679.

Jensen, R. O., K. Winzer, et al. (2008). "Differential recognition of *Staphylococcus aureus* quorum-sensing signals depends on both extracellular loops 1 and 2 of the transmembrane sensor AgrC." J. Mol. Biol. **381**(2): 300-309.

Ji, G., R. Beavis, et al. (1997). "Bacterial interference caused by autoinducing peptide variants." Science **276**(5321): 2027-2030.

Ji, G., R. C. Beavis, et al. (1995). "Cell density control of *Staphylococcal* virulence mediated by an octapeptide pheromone." PNAS USA **92**(26): 12055-12059.

Johnson, S. W., S. F. Jenkinson, et al. (2004). "Oxetane cis- and trans-[beta]-amino-acid scaffolds from L-rhamnose by efficient SN2 reactions in oxetane rings; pseudoenantiomeric analogues of the antibiotic oxetin." Tetrahedron: Asymm. **15**(17): 2681-2686.

Johnston, J. N., H.-C. Tsui, et al. (1998). "Application of an S → O allylic transposition in the context of a bridgehead olefinic system. New opportunities for the

structural modification of bicyclo[6.2.1]undecanes via transannular ring closure." J. Org. Chem. **63**(1): 129-136.

Jones, M. B., R. Jani, et al. (2005). "Inhibition of *Bacillus anthracis* growth and virulence-gene expression by inhibitors of quorum-sensing." J. Infect. Dis. **191**(11): 1881-1888.

Jung, M. E. and C. J. Nichols (1996). "Highly stereoselective synthesis of trans,trans-4-aryl-2,3-oxetanedimethanols: Preparation of oxetanocin a analogues." Tetrahedron Lett. **37**(43): 7667-7670.

Kalvin, D. M. and R. W. Woodard (1985). "Synthesis of (4R)-D,L-[4-2H]- and (4S)-D,L-[42H]homoserine lactones." J. Org. Chem. **50**(13): 2259-2263.

Katsuki, T. and K. B. Sharpless (1980). "The first practical method for asymmetric epoxidation." J. Am. Chem. Soc. **102**(18): 5974-5976.

Kaufmann, G. F., R. Sartorio, et al. (2006). "Antibody interference with N-acyl homoserine lactone-mediated bacterial quorum sensing." J. Am. Chem. Soc. **128**(9): 2802-2803.

Kaufmann, G. F., R. Sartorio, et al. (2005). "Revisiting quorum sensing: Discovery of additional chemical and biological functions for 3-oxo-N-acylhomoserine lactones." PNAS USA **102**(2): 309-314.

Kawahata, Y., S. Takatsuto, et al. (1986). "Synthesis of a new amino acid antibiotic, oxetin, and its three stereoisomers." Chem. Pharm. Bull. **34**(8): 3102-3110.

Khan, F. A., J. Dash, et al. (2005). "Concise synthesis of novel oxa-bridged compounds." J. Org. Chem. **70**(19): 7565-7577.

Kies, S., C. Vuong, et al. (2003). "Control of antimicrobial peptide synthesis by the agr quorum sensing system in *Staphylococcus epidermidis*: activity of the lantibiotic epidermin is regulated at the level of precursor peptide processing." Peptides **24**(3): 329-338.

Kim, H., H. Lee, et al. (2007). "Asymmetric total syntheses of (+)-3-(Z)-laureatin and (+)-3-(Z)-isolaureatin by “lone pair−lone pair interaction-controlled” isomerization." J. Am. Chem. Soc. **129**(8): 2269-2274.

Kim, M. H., W.-C. Choi, et al. (2005). "The molecular structure and catalytic mechanism of a quorum-quenching N-acyl-L-homoserine lactone hydrolase." PNAS USA **102**(49): 17606-17611.

Kiratisin, P. and S. Sanmee (2008). "Roles andinteractions of *Burkholderia pseudomallei* BpsIR quorum-sensing system determinants." J. Bacteriol. **190**(21): 7291-7297.

Kirwan, J. P., T. A. Gould, et al. (2006). "Quorum-sensing signal synthesis by the *Yersinia pestis* acyl-homoserine lactone synthase YspI." J. Bacteriol. **188**(2): 784-788.

Kitayama, T., R. Iwabuchi, et al. (2007). "Synthesis of a novel inhibitor against MRSA and VRE: Preparation from zerumbone ring opening material showing histidine-kinase inhibition." Bioorg. Med. Chem. Lett. **17**(4): 1098-1101.

Kitayama, T., R. Iwabuchi, et al. (2004). "Unprecedented olefin-dependent histidine-kinase inhibitory of zerumbone ring-opening material." Bioorg. Med. Chem. Lett. **14**(23): 5943-5946.

Kleerebezem, M. (2004). "Quorum sensing control of lantibiotic production; nisin and subtilin autoregulate their own biosynthesis." Peptides **25**(9): 1405-1414.

Kleerebezem, M. Q., L. E. N. Kuipers, O. P. De Vos, W. M. (1997). "Quorum sensing by peptide pheromones and two-component signal-transduction systems in Gram-positive bacteria." Mol. Microbiol. **24**(5): 895-904.

Koenig, R. L., J. L. Ray, et al. (2004). "*Staphylococcus aureus* AgrA binding to the RNAIII-agr regulatory region." J. Bacteriol. **186**(22): 7549-7555.

Kotick, M. P., D. L. Leland, et al. (1983). "Analgesic narcotic antagonists. 15. Potent narcotic agonist 7-.beta.-arylalkyl-4,5.alpha.-epoxymorphinans." J. Med. Chem. **26**(7): 1050-1056.

Krasovskiy, A. and P. Knochel (2004). "A LiCl-mediated Br/Mg exchange reaction for the preparation of functionalized aryl- and heteroarylmagnesium compounds from organic bromides." Angew. Chem. Int. Ed. **43**(25): 3333-3336.

Krylova, O. V., V. N. Elokhina, et al. (2001). "Vicarious C-amination of nitrobenzene." Rus. J. Org. Chem. **37**(6): 887-888.

Kumar, A. and H. P. Schweizer (2005). "Bacterial resistance to antibiotics: Active efflux and reduced uptake." Adv. Drug Del. Rev. **57**(10): 1486-1513.

Kurosawa, E., A. Furusaki, et al. (1973). "The absolute configurations of laureatin and isolaureatin." Tetrahedron Lett. **14**(39): 3857-3860.

Kwang-Nym Cho, S.-J. P., and Kee-In Lee (2004). "A facile synthesis of 2-chloro-5,7-dihydro-pyrrolo[3,4-b]pyridine-6-carboxamidine, an annulated nicotinoid." Bull. Korean Chem. Soc. **25**(6): 924-926.

Lakshmipathi, P., D. Grée, et al. (2002). "A facile C−C bond cleavage in the epoxides and its use for the synthesis of oxygenated heterocycles by a ring expansion strategy." Org. Lett. **4**(3): 451-454.

Leland, D. L. and M. P. Kotick (1983). "Analgesic narcotic antagonists. Part 13. 7.alpha.- or 7.beta.-(4-Phenylbutyl)dihydrocodeine derivatives." J. Org. Chem. **48**(11): 1813-1819.

Lewenza, S., B. Conway, et al. (1999). "Quorum Sensing in *Burkholderia cepacia*: Identification of the LuxRI homologs CepRI." J. Bacteriol. **181**(3): 748-756.

Li, C., D. Lee, et al. (2005). "A hexacyclic ent-trachylobane diterpenoid possessing an oxetane Ring from *Mitrephora glabra*." Org. Lett. **7**(25): 5709-5712.

Lina, G., S. Jarraud, et al. (1998). "Transmembrane topology and histidine protein kinase activity of AgrC, the agr signal receptor in *Staphylococcus aureus*." Mol. Microbiol. **28**(3): 655-662.

Liu, Q. and Y. Tor (2003). "Simple conversion of aromatic amines into azides." Org. Lett. **5**(14): 2571-2572.

Loh, J., Carlson, R.W., York, W.S., Stacey, G. (2002) Bradyoxetin, a unique chemical signal involved in symbiotic gene regulation. PNAS USA, **99**, 14446-14451.

Lupp, C. and E. G. Ruby (2004). "*Vibrio fischeri* LuxS and AinS: Comparative study of two signal synthases." J. Bacteriol. **186**(12): 3873-3881.

Lyon, G. J., P. Mayville, et al. (2000). "Rational design of a global inhibitor of the virulence response in *Staphylococcus aureus*, based in part on localization of the

site of inhibition to the receptor-histidine kinase, AgrC." PNAS USA **97**(24): 13330-13335.

Lyon, G. J. and T. W. Muir (2003). "Chemical signaling among bacteria and its inhibition." Chemistry & Biology **10**(11): 1007-1021.

Lyon, G. J., J. S. Wright, et al. (2002). "Key determinants of receptor activation in the agr autoinducing peptides of *Staphylococcus aureus*." Biochemistry **41**(31): 10095-10104.

Makosza, M. and A. Kwast (1998). "Vicarious nucleophilic substitution of hydrogen. Mechanism and orientation." J. Phys. Org. Chem. **11**(5): 341-349.

Makosza, M. and R. Podraza (2000). "Hydroxylation and amination of Azulenes by vicarious nucleophilic substitution of hydrogen." Eur. J. Org. Chem. (1): 193-198.

Makosza, M. and K. Sienkiewicz (1998). "Hydroxylation of nitroarenes with alkyl hydroperoxide anions via vicarious nucleophilic substitution of hydrogen." J. Org. Chem. **63**(13): 4199-4208.

Manabe, S., N. Enoki, et al. (1985). "Application of the cd homoallylic benzoate method as a chiroptical tool for determination of absolute configuration." Tetrahedron Lett. **26**(18): 2213-2216.

Manefield, M., T. B. Rasmussen, et al. (2002). "Halogenated furanones inhibit quorum sensing through accelerated LuxR turnover." Microbiology **148**(4): 1119-1127.

Mansour, T. S., P. A. Bradford, et al. (2008). Chapter 15 Recent Developments in [beta]-Lactamases and Inhibitors. Ann. Rep. Med. Chem. E. M. John, Academic Press. **Volume 43:** 247-267.

Marketon, M. M., M. R. Gronquist, et al. (2002). "Characterization of the *Sinorhizobium meliloti* sinR/sinI locus and the production of novel N-acyl homoserine lactones." J. Bacteriol. **184**(20): 5686-5695.

Martinelli, M. J., N. K. Nayyar, et al. (1999). "Dibutyltin oxide catalyzed selective sulfonylation of alpha-chelatable primary alcohols." Org. Lett. **1**(3): 447-450.

Mayville, P., G. Ji, et al. (1999). "Structure-activity analysis of synthetic autoinducing thiolactone peptides from *Staphylococcus aureus* responsible for virulence." PNAS USA **96**(4): 1218-1223.

McClean, K. H., M. K. Winson, et al. (1997). "Quorum sensing and *Chromobacterium violaceum*: Exploitation of violacein production and inhibition for the detection of N-acylhomoserine lactones." Microbiology **143**(12): 3703-3711.

McDowell, P., Z. Affas, et al. (2001). "Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of *Staphylococcus aureus*." Mol. Microbiol. **41**(2): 503-512.

Milton, D., A. Hardman, et al. (1997). "Quorum sensing in *Vibrio anguillarum:* characterization of the vanI/vanR locus and identification of the autoinducer N-(3-oxodecanoyl)-L- homoserine lactone." J. Bacteriol. **179**(9): 3004-3012.

Mordini, A., S. Bindi, et al. (2001). "Stereoselective access to hydroxy oxetanes and tetrahydrooxepines through isomerization of oxiranyl ethers." J. Org. Chem. **66**(9): 3201-3205.

Mosimann, H. a. V., P. (2000). "Oxetane formation by 1,3-migration of benzyloxy group in 7-oxabicyclo[2.2.1]hept-2-yl cations: Synthesis of 4,7-dioxatricyclo[3.2.1.03,6] octane and 2-oxabicyclo[2.2.2]octane encrusted in the 1,4:5,8-diepoxy-perhydrophenanthrene ring system." Heterocycles **52**(1): 171-183.

N. K. Christensen, A. K. L. A., T. R. Schultz and P. Nielsen (2003). "Synthesis of hydroxymethyl branched [3.2.0]bicyclic nucleosides using a regioselective oxetane ring-formation." Org. Biomol. Chem. **1**: 3738 - 3748.

Nyffeler, P. T., C. H. Liang, et al. (2002). "The chemistry of amine-azide interconversion: Catalytic diazotransfer and regioselective azide reduction." J. Am. Chem. Soc. **124**(36): 10773-10778.

Omura, S., M. Murata, et al. (1984). "Oxetin, a new antimetabolite from an actinomycete. Fermentation, isolation, structure and biological activity." J. Antibiotics **37**(11): 1324-1332.

Østergaard, S. and A. Holm (1997). "Peptomers: A versatile approach for the preparation of diverse combinatorial peptidomimetic bead libraries." Mol. Div. **3**(1): 17-27.

Paquette, L. A., S. D. Edmondson, et al. (1999). "Studies directed toward the synthesis of the unusual antileukemic diterpene Jatrophatrione. 2. Functionalization of advanced polycyclic precursors to the 9-epi and 8,9-dehydro congeners." J. Org. Chem. **64**(9): 3255-3265.

Park, J., R. Jagasia, et al. (2007). "Infection control by antibody disruption of bacterial quorum sensing signaling." Chem. Biol. **14**(10): 1119-1127.

Park, K. K., C. H. Oh, et al. (1993). "Sodium dithionite reduction of nitroarenes using viologen as an electron phase-transfer catalyst." Tetrahedron Lett. **34**(46): 7445-7446.

Parsek, M. R. and E. P. Greenberg (2000). "Acyl-homoserine lactone quorum sensing in Gram-negative bacteria: A signaling mechanism involved in associations with higher organisms." PNAS **97**(16): 8789-8793.

Patch, J. A. K., K.; Seurynck, S. L.; Zuckermann, R. N.; and Barron, A. E. (2004). Versatile Oligo(N-Substituted) Glycines: The Many Roles of Peptoids in Drug Discovery. Weinheim, Germany, WILEY-VCH Verlag GmbH & Co. KGaA.

Peng , H. L. (1988). "Cloning, characterization, and sequencing of an accessory gene regulator (agr) in Staphylococcus aureus. ." J. Bacteriology **170**(9): 4365-4372.

Pesci, E. C., J. B. J. Milbank, et al. (1999). "Quinolone signaling in the cell-to-cell communication system of *Pseudomonas aeruginosa*." PNAS **96**(20): 11229-11234.

Pestova, E. V., L. S. Havarstein, et al. (1996). "Regulation of competence for genetic transformation in *Streptococcus pneumoniae* by an auto-induced peptide pheromone and a two-component regulatory system." Mol.Microbiol. **21**(4): 853-862.

Platonov, A. Y., A. N. Evdokimov, et al. (2002). "Solubility of potassium carbonate and potassium hydrocarbonate in methanol." J. Chem. Eng. Data **47**(5): 1175-1176.

Pomianek, M. E. and M. F. Semmelhack (2007). "Making bacteria behave: New agonists and antagonists of quorum sensing." ACS Chem. Biol. **2**(5): 293-295.

Prange, T., M. S. Rodriguez, et al. (2003). "Synthesis of phytuberin. 4-endo-tet acid-catalyzed cyclization of α-hydroxy epoxides." J. Org. Chem. **68**(11): 4422-4431.

Prasad, K. R. and A. Chandrakumar (2007). "Stereoselective synthesis of cytotoxic anhydrophytosphingosine Pachastrissamine [Jaspine B]." J. Org. Chem. **72**(16): 6312-6315.

Proemmel, S., R. Wartchow, et al. (2002). "Synthesis and studies of marine natural products: the dictyoxetane core from 8-oxabicyclo[3.2.1]oct-6-en-3-ones." Tetrahedron **58**(31): 6199-6206.

Pullaiah, K. C., R. K. Surapaneni, et al. (1985). "Dictyoxetane, a novel diterpene from the brown alga *Dictyota dichotoma* from the Indian Ocean." J. Org. Chem. **50**(19): 3665-3666.

Puskas, A., E. Greenberg, et al. (1997). "A quorum-sensing system in the free-living photosynthetic bacterium Rhodobacter sphaeroides." J. Bacteriol. **179**(23): 7530-7537.

Qin, X., K. V. Singh, et al. (2000). "Effects of *Enterococcus faecalis* fsr genes on production of gelatinase and a serine protease and virulence." Infect. Immun. **68**(5): 2579-2586.

Qiu, R., W. Pei, et al. (2005). "Identification of the putative *Staphylococcal* AgrB catalytic residues involving the proteolytic cleavage of AgrD to generate autoinducing peptide." J. Biol. Chem. **280**(17): 16695-16704.

R. C. A. Isaacs, M. J. D. G., S. J. Danishefsky (1993). "Synthesis of an enantiomerically pure intermediate containing the CD substructure of taxol." J. Org. Chem. **58**(15): 3938-3941.

Rao, C. B., K. C. Pullaiah, et al. (1986). "The diterpenes of *Dictyota dichotoma* from the Indian Ocean." J. Org. Chem. **51**(14): 2736-2742.

Rebstock, M. C., H. M. Crooks, Jr., et al. (1949). "Chloramphenicol (chloromycetin). IV. Chemical studies." J. Am. Chem. Soc. **71**: 2458-2462.

Regitz, M. (1967). "New methods of preparative organic chemistry. Transfer of diazo groups." Angew. Chem. Int. Ed. Eng. **6**(9): 733-749.

Rofoo, M., M.-C. Roux, et al. (2001). "Preparation of oxetanes by silicon-directed 4-exo trig electrophilic cyclisations of homoallylic alcohols." Tetrahedron Lett. **42**(13): 2481-2484.

Roychoudhury, S., N. A. Zielinski, et al. (1993). "Inhibitors of two-component signal transduction systems: inhibition of alginate gene activation in *Pseudomonas aeruginosa.*" PNAS USA **90**(3): 965-969.

Rumbaugh, K. (2007). "Convergence of hormones and autoinducers at the host/pathogen interface." Anal. Bioanal. Chem. **387**(2): 425-435.

Saphier, S., Y. Hu, et al. (2004). "Origin of selectivity in the antibody 20F10-catalyzed Yang cyclization." J. Am. Chem. Soc. **127**(1): 132-145.

Sarma, A. S. and P. Chattopadhyay (1982). "Synthetic studies of trans-clerodane diterpenoids and congeners: stereocontrolled total synthesis of (.+-.)-avarol." J. Org. Chem. **47**(9): 1727-1731.

Sasaki, M., N. Matsumori, et al. (1995). "Stereochemical assignment of the C35-C39 Acyclic linkage in maitotoxin: completion of stereochemical determination of C15-C134." Tetrahedron Lett. **36**(49): 9011-9014.

Sasaki, M., K. Tanino, et al. (2003). "The C2 selective nucleophilic substitution reactions of 2,3-epoxy alcohols mediated by trialkyl borates: The First *endo*-Mode epoxide-opening reaction through an intramolecular metal chelate." Org. Lett. **5**(10): 1789-1791.

Sayyed, I. A. and Sudalai, A. "Asymmetric synthesis of L-DOPA and (*R*)-selegiline via, OsO_4-catalyzed asymmetric dihydroxylation." Tetrahedrom: *Asymmetry* **15** (2004) 3111-3116

Schaefer, A., B. Hanzelka, et al. (1996). "Quorum sensing in *Vibrio fischeri:* probing autoinducer-LuxR interactions with autoinducer analogs." J. Bacteriol. **178**(10): 2897-2901.

Schaefer, A. L., D. L. Val, et al. (1996). "Generation of cell-to-cell signals in quorum sensing: acyl homoserine lactone synthase activity of a purified *Vibrio fischeri* LuxI protein." PNAS USA **93**(18): 9505-9509.

Schneider, C. (2000). "Quaternary ammonium salt catalyzed azidolysis of epoxides with Me3SiN3." Synlett(12): 1840–1842.

Schripsema, J., K. de Rudder, et al. (1996). "Bacteriocin small of *Rhizobium leguminosarum* belongs to the class of N- acyl-L-homoserine lactone molecules, known as autoinducers and as quorum sensing co-transcription factors." J. Bacteriol. **178**(2): 366-371.

Shigenaga, A., Moss, J.A., Ashley, F.T., Kaufmann, G.F., and and K. D. Janda (2006). "Solid-phase synthesis and cyclative cleavage of quorum sensing depsipeptide analogues by acylphenyldiazene activation." Synlett(4): 551–554.

Shioiri, T. M., F.; Hamada, Y. (1994). "Use of the aryl groups as the carboxyl synthon. Application to the synthesis of some natural products containing hydroxy amino acid functions." Pure and App. Chem. **66**(10-11): 2151-2154.

Sieh, D. H., D. J. Wilbur, et al. (1980). "Preparation of trialkyltriazenes. A comparison of the nitrogen-nitrogen bond rotation in trialkyltriazenes and aryldialkyltriazenes by variable temperature carbon-13 NMR." J. Am. Chem. Soc. **102**(11): 3883-3887.

Smith, K. M., Y. Bu, et al. (2003). "Induction and inhibition of *Pseudomonas aeruginosa* Quorum sensing by synthetic autoinducer analogs." Chem. Biol. **10**(1): 81-89.

Smith, M. B. M., J. (2007). March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Wiley.

Smith, R. S., S. G. Harris, et al. (2002). "The *Pseudomonas aeruginosa* quorum-sensing molecule N-(3-oxododecanoyl)homoserine lactone contributes to virulence and induces inflammation *in vivo*." J. Bacteriol. **184**(4): 1132-1139.

Smith, R. S. and B. H. Iglewski (2003). "*Pseudomonas aeruginosa* quorum sensing as a potential antimicrobial target." J. Clin. Invest. **112**(10): 1460-1465.

Sokol, P. A., U. Sajjan, et al. (2003). "The CepIR quorum-sensing system contributes to the virulence of *Burkholderia cenocepacia* respiratory infections." Microbiol. **149**(12): 3649-3658.

Solsona, J. G., P. Romea, et al. (2003). "Studies directed toward the construction of the polypropionate fragment of superstolide A." Org. Lett **5**(24): 4681-4684.

Stalewski, J. (1998). "The vicarious nucleophilic substitution of hydrogen proceeding via a cyclopropane ring-opening." Tetrahedron Lett. **39**(51): 9523-9526.

Steidle, A., M. Allesen-Holm, et al. (2002). "Identification and characterization of an N-acylhomoserine lactone-dependent quorum-sensing system in *Pseudomonas putida* strain IsoF." Appl. Environ. Microbiol. **68**(12): 6371-6382.

Sugimoto, M., T. Suzuki, et al. (2007). "The first total synthesis of (+)-(Z)-laureatin." Tetrahedron Lett. **48**(7): 1109-1112.

Swift, S., A. Karlyshev, et al. (1997). "Quorum sensing in *Aeromonas hydrophila* and *Aeromonas salmonicida*: Identification of the LuxRI homologs AhyRI and AsaRI and their cognate N-acylhomoserine lactone signal molecules." J. Bacteriol. **179**(17): 5271-5281.

Tatibouet, A., Lefoix, M., Nadolny, J., Martin, O. R., Rollin P., Yang, J., Holman G. D.;" D-Fructose–L-sorbose interconversions. Access to 5-thio-D-fructose and interaction with the D-fructose transporter, GLUT5" Carbohydrate Research 333 (2001) 327-334.

Telford, G. W., D.; Williams, P.; Tomkins, P. T.; Appleby, P.; Sewell, H.; Stewart, G. S. A. B.; Bycroft, B. W.; Pritchard, D. I. (1998). "The *Pseudomonas aeruginosa* quorum-sensing signal molecule N-(3-oxododecanoyl)-L-homoserine lactone has immunomodulatory activity." Inf. Immun. **66**(1): 36-42.

Tino J. A., L. M. D., Kishi Y. (1987). "A new, efficient synthesis of the left half of narasin." Heterocycles **25**(1): 97-104.

Toyota*, M., M. Rudyanto, et al. (2000). "Application of palladium-catalyzed cycloalkenylation reaction to terpenoid synthesis--novel approach to tricyclo[5.3.1.02,6]undecane derivative and its transformation into bicyclo[5.3.1]undecane ring system." Tetrahedron Lett. **41**(46): 8929-8932.

Ulbrich, H. K., A. Luxenburger, et al. (2006). "A novel class of potent nonglycosidic and nonpeptidic pan-selectin inhibitors." J. Med. Chem. **49**(20): 5988-5999.

Ulrich, R. L., D. DeShazer, et al. (2004). "Role of quorum sensing in the pathogenicity of *Burkholderia pseudomallei*." J. Med.Microbiol. **53**(11): 1053-1064.

Uttaro, J.-P., G. Audran, et al. (2005). "Chemoenzymatic taxanes approach using both enantiomers of the same building block. 2. Taxol CD ring unit." J. Org. Chem. **70**(9): 3484-3489.

Vannini, A., C. Volpari, et al. (2004). "Crystallization and preliminary X-ray diffraction studies of the quorum-sensing regulator TraM from *Agrobacterium tumefaciens*." Acta Cryst. Sec. D **60**(1): 146-148.

Vannini, A., C. Volpari, et al. (2002). "The crystal structure of the quorum sensing protein TraR bound to its autoinducer and target DNA." EMBO J. **21**(17): 4393-4401.

Varga J., S., V. L. and Melville, S. B. (2004). "The CcpA protein is necessary for efficient sporulation and enterotoxin gene (cpe) regulation in *Clostridium perfringens*." J. Bacteriol. **186**(16): 5221-5229.

Vasella, A., C. Witzig, et al. (1991). "Convenient synthesis of 2-azido-2-deoxy-aldoses by diazo transfer." Helv. Chim. Acta **74**(8): 2073-2077.

von Bodman, S. B., D. R. Majerczak, et al. (1998). "A negative regulator mediates quorum-sensing control of exopolysaccharide production in *Pantoea stewartii* subsp. stewartii." PNAS USA **95**(13): 7687-7692.

Wang, G., Y. Wang, et al. (1999). "1-Iodomethyl-3,4-diphenyl-2,6-dioxabicyclo[2.2.0]hexane: the first example of a [2.2.0] fused ketal." Tetrahedron Lett. **40**(39): 7051-7053.

Welch, M., D. E. Todd, et al. (2000). "N-acyl homoserine lactone binding to the CarR receptor determines quorum-sensing specificity in Erwinia." EMBO J. **19**(4): 631-641.

Wempe, M. F. and J. R. Grunwell (1995). "The transannular rearrangement of 5-cyclodecynone." J. Org. Chem. **60**(9): 2714-2720.

Wendling, F. and M. Miesch (2001). "Unexpected reactivity of acetylenic ω-ketoesters toward TBAF and t-BuOK; New cascade reactions affording allene and oxetane derivatives." Org. Lett. **3**(17): 2689-2691.

Williams, P. (2007). "Quorum sensing, communication and cross-kingdom signalling in the bacterial world." Microbiol. **153**(12): 3923-3938.

Wright, J. S., G. J. Lyon, et al. (2004). "Hydrophobic interactions drive ligand-receptor recognition for activation and inhibition of staphylococcal quorum sensing." PNAS USA **101**(46): 16168-16173.

Wu, B. and H. S. Mosher (1986). "Configuration of some para-substituted benzhydrols." J. Org. Chem. **51**(10): 1904-1906.

Xian-Zhi, L. and H. Nikaido (2009). "Efflux-mediated drug resistance in bacteria." Drugs **69**(12): 1555-1623.

Xiao, X., P. Yu, et al. (2007). "A Cell-permeable synthetic transcription factor mimic." Angew. Chem. Int. Ed. **46**(16): 2865-2868.

Xin, C., S. Schauder, et al. (2002). "Structural identification of a bacterial quorum-sensing signal containing boron." Nature **415**(6871): 545.

Yajima, A., A. A. N. van Brussel, et al. (2008). "Synthesis and stereochemistry-activity relationship of small bacteriocin, an autoinducer of thesymbiotic nitrogen-fixing bacterium *Rhizobium leguminosarum*." Org. Lett. **10**(10): 2047-2050.

Yamamoto, K., T. Kitayama, et al. (2001). "Antibacterial agents that inhibit histidine protein kinase YycG of *Bacillus subtilis*." Biosci. Biotech. Biochem. **65**(10): 2306-2310.

Yan, R.-B., F. Yang, et al. (2005). "An efficient and improved procedure for preparation of triflyl azide and application in catalytic diazotransfer reaction." Tetrahedron Lett. **46**(52): 8993-8995.

Zapun, A., C. Contreras-Martel, et al. (2008). "Penicillin-binding proteins and β-lactam resistance." FEMS Microbiol. Rev. **32**(2): 361-385.

Zhang, H.-B., L.-H. Wang, et al. (2002). "Genetic control of quorum-sensing signal turnover in *Agrobacterium tumefaciens*." PNAS USA **99**(7): 4638-4643.

Zhang, L., L. Gray, et al. (2002). "Transmembrane topology of AgrB, the protein involved in the post-translational modification of AgrD in *Staphylococcus aureus*." J. Biol. Chem. **277**(38): 34736-34742.

Zhang, L., J. Lin, et al. (2004). "Membrane anchoring of the AgrD N-terminal amphipathic region is required for its processing to produce a quorum-sensing pheromone in *Staphylococcus aureus*." J. Biol. Chem. **279**(19): 19448-19456.

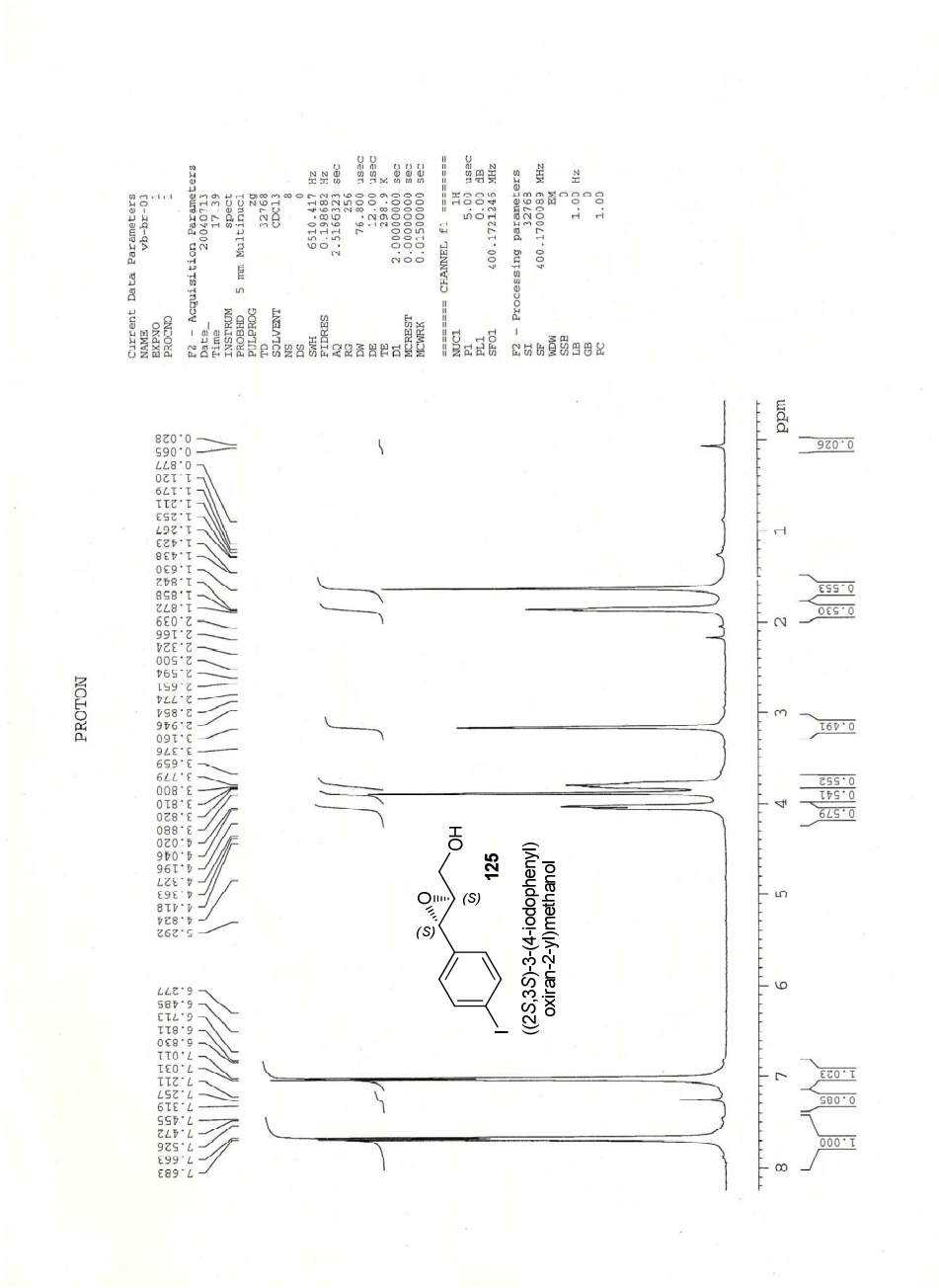
Zhang, R.-g., T. Pappas, et al. (2002). "Structure of a bacterial quorum-sensing transcription factor complexed with pheromone and DNA." Nature **417**(6892): 971-974.

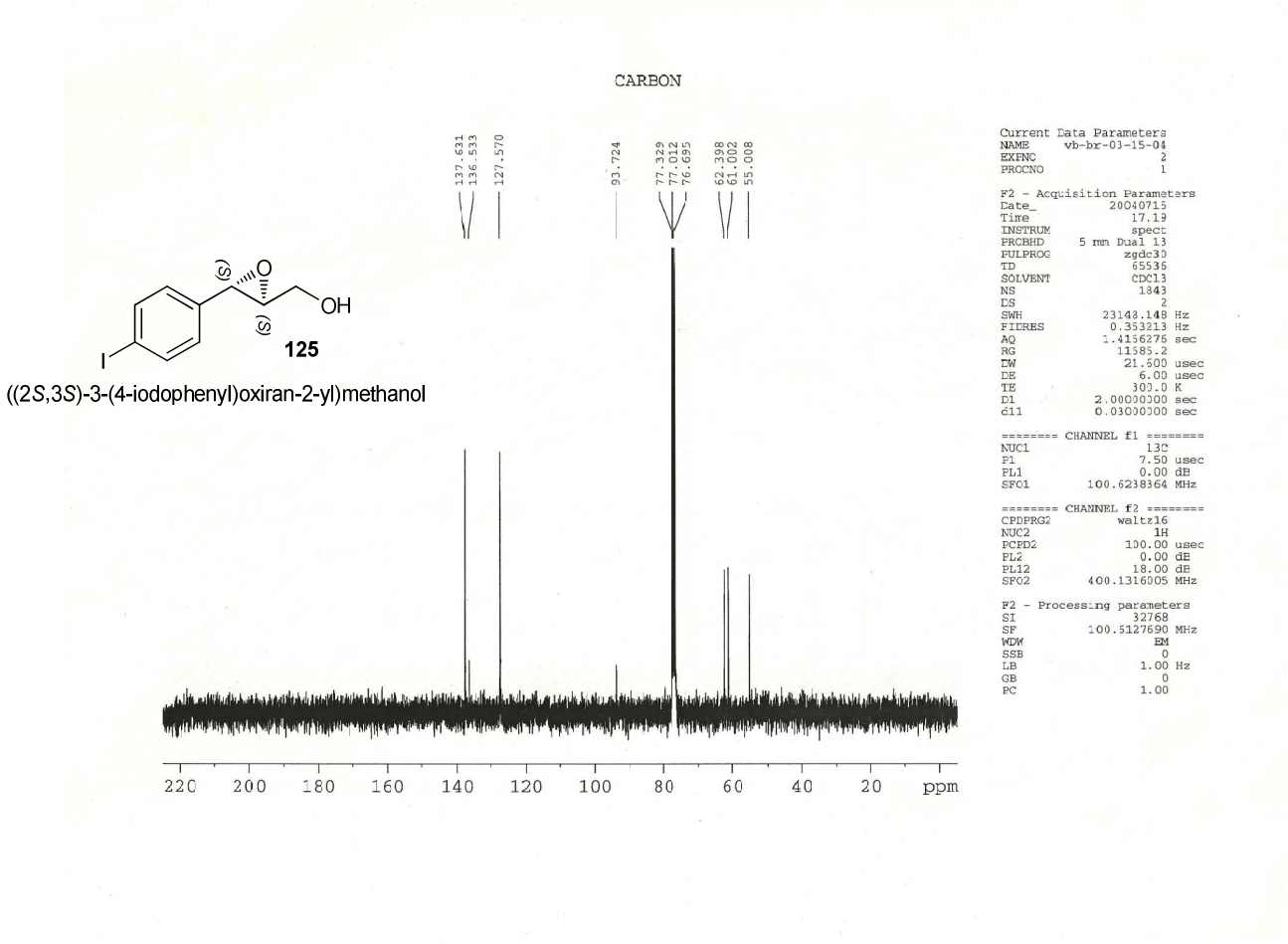
Zhang, Z. and L. S. Pierson, III (2001). "A second quorum-sensing system regulates cell surface properties but not phenazine antibiotic production in *Pseudomonas aureofaciens*." Appl. Environ. Microbiol. **67**(9): 4305-4315.

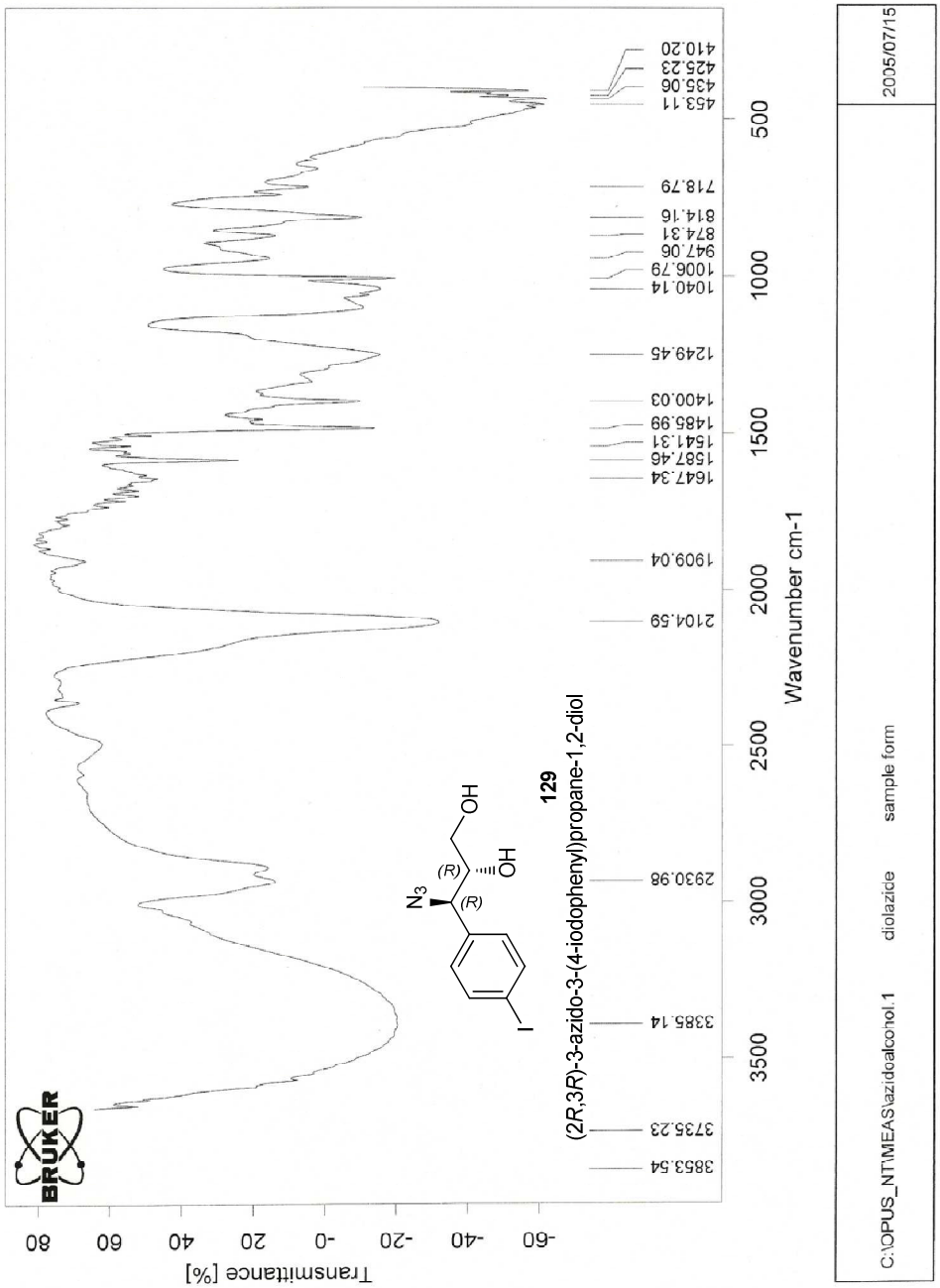
Zhao, M., J. Li, et al. (1998). "A novel chromium trioxide catalyzed oxidation of primary alcohols to the carboxylic acids." Tetrahedron Lett. **39**(30): 5323-5326.

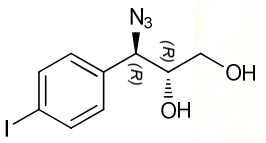
Zhu, J. and S. C. Winans (2001). "The quorum-sensing transcriptional regulator TraR requires its cognate signaling ligand for protein folding, protease resistance, and dimerization." PNAS USA **98**(4): 1507-1512.

Zou, W., M. Sandbhor, et al. (2007). "Stereoselective synthesis of polyhydroxylated quinolizidines from C-glycosides by one-pot double-conjugate addition." J. Org. Chem. **72**(4): 1226-1234.


PROTON
Current Data Parameters
NAME vb-br-03
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040713
Time 17.39
INSTRUM spect
PROBHD 5 mm Multinuci
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 6510.417 Hz
FIDRES 0.198682 Hz
AQ 2.5166323 sec
RG 256
DW 76.800 usec
DE 12.00 usec
TE 298.9 K
D1 2.0000000 sec
MCREST 0.0000000 sec
MCWRK 0.0150000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 5.00 usec
PL1 0.00 dB
SFO1 400.1721245 MHz
F2 - Processing parameters
SI 32768
SF 400.1700089 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OH
(S)
(S)
O
I
125
((2S,3S)-3-(4-iodophenyl)
oxiran-2-yl)methanol
ppm

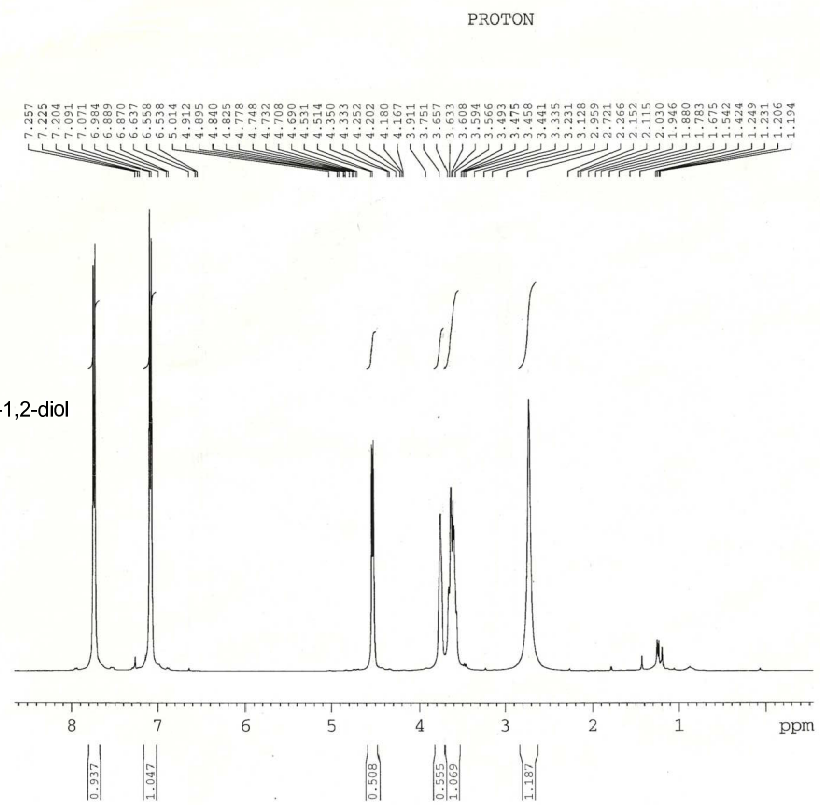

CARBON
137.631
136.533
127.570
93.724
77.329
77.012
76.695
62.398
61.002
55.008
O
OH
(S)
(S)
I
125
((2S,3S)-3-(4-iodophenyl)oxiran-2-yl)methanol
220
200
180
160
140
120
100
80
60
40
20
ppm
Current Data Parameters
NAME vb-br-03-15-04
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040715
Time 17.19
INSTRUM spect
PROBHD 5 mm Dual 13
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 1843
DS 2
SWH 23148.148 Hz
FIDRES 0.353213 Hz
AQ 1.4156275 sec
RG 11585.2
DW 21.600 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.50 usec
PL1 0.00 dB
SFO1 100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 18.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.5127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00


BRUKER
Transmittance [%]
80
60
40
20
-0
-20
-40
-60
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
3853.54
3735.23
3385.14
2930.98
2104.59
1909.04
1647.34
1587.46
1541.31
1485.99
1400.03
1249.45
1040.14
1006.79
947.06
874.31
814.16
718.79
453.11
435.06
425.23
410.20
129
(2R,3R)-3-azido-3-(4-iodophenyl)propane-1,2-diol
OH
OH
(R)
(R)
N3
I
C:\OPUS_NT\MEAS\azidoalcohol.1
diolazide
sample form
2005/07/15
Page 1/1

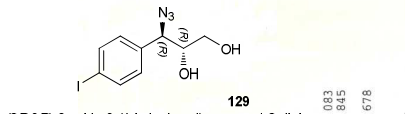


129

(2*R*,3*R*)-3-azido-3-(4-iodophenyl)propane-1,2-diol



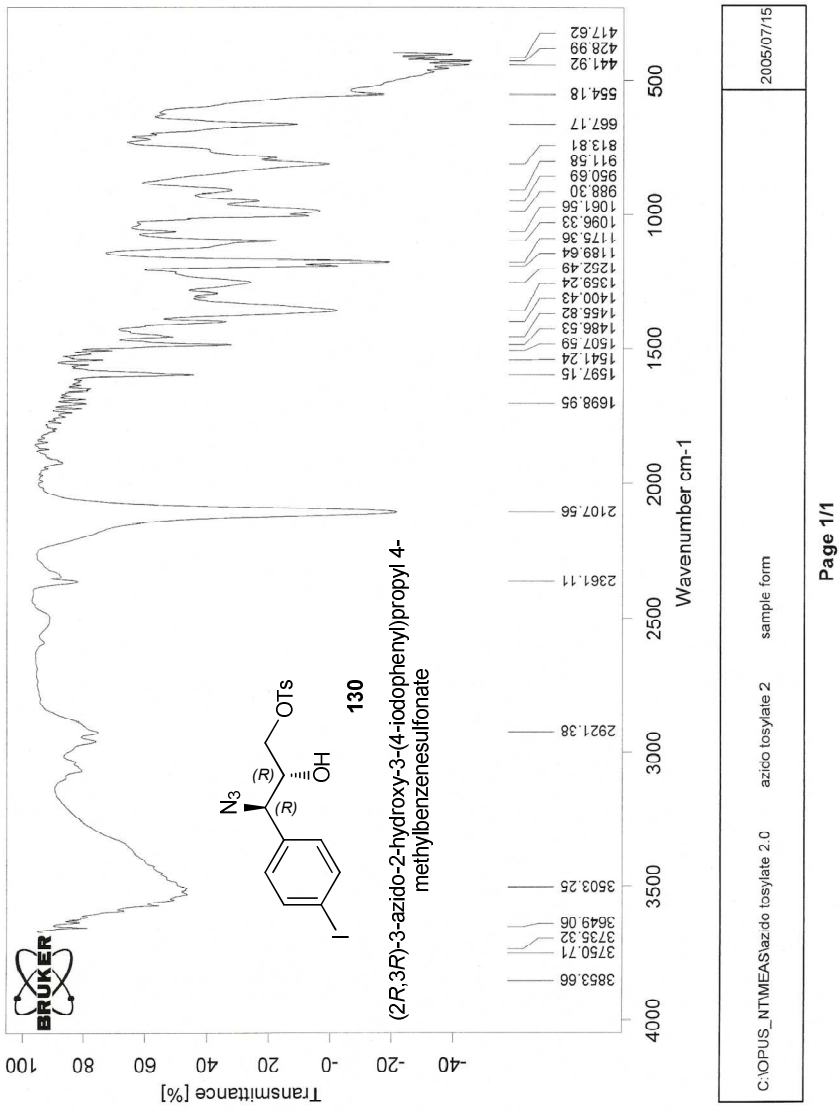

```
Current Data Parameters
NAME       vb-br-04-6-10
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20040721
Time               19.18
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG               zg
TD                 32768
SOLVENT            CDCl3
NS                     8
DS                     0
SWH             6510.417 Hz
FIDRES          0.198682 Hz
AQ              2.5166323 sec
RG                    64
DW                76.800 usec
DE                12.00 usec
TE                296.6 K
D1             2.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 5.00 usec
PL1                0.00 dB
SFO1         400.1721246 MHz

F2 - Processing parameters
SI                 32768
SF           400.1700089 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.00
```

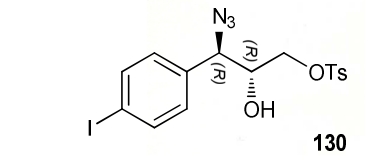


129

(2*R*,3*R*)-3-azido-3-(4-iodophenyl)propane-1,2-diol

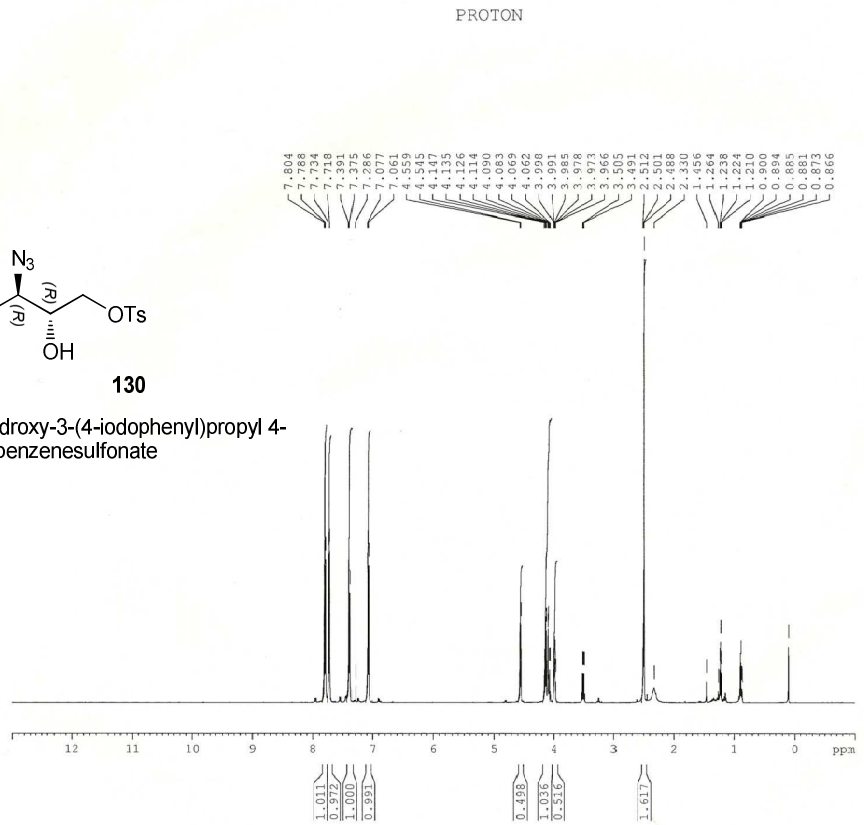

```
Current Data Parameters
NAME          vb-br-04-6-10
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20040722
Time                  14.33
INSTRUM                spect
PROBHD     5 mm Dual 13
PULPROG             zgdc30
TD                   65536
SOLVENT              CDCl3
NS                    1000
DS                       2
SWH              23148.148 Hz
FIDRES           0.353213 Hz
AQ               1.4156276 sec
RG                  11585.2
DW                  21.600 usec
DE                   6.00 usec
TE                  300.0 K
D1               2.00000000 sec
d11              0.03000000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                   7.50 usec
PL1                  0.00 dB
SFO1          100.6238364 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2              100.00 usec
PL2                  0.00 dB
PL12                18.00 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                     32768
SF            100.6127690 MHz
WDW                       EM
SSB                        0
LB                   1.00 Hz
GB                         0
PC                   1.00
```


Transmittance [%]
100
80
60
40
20
0
-20
-40
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
3853.66
3750.71
3735.32
3649.06
3503.25
2921.38
2361.11
2107.56
1698.95
1597.15
1541.24
1507.59
1486.53
1455.82
1400.43
1359.24
1252.49
1189.64
1175.36
1096.33
1061.56
988.30
950.69
911.58
813.81
667.17
554.18
441.92
428.99
417.62
OTs
OH
N3
(R)
(R)
I
130
(2R,3R)-3-azido-2-hydroxy-3-(4-iodophenyl)propyl 4-methylbenzenesulfonate
C:\OPUS_NT\MEAS\azido tosylate 2.0
azido tosylate 2
sample form
2005/07/15
Page 1/1



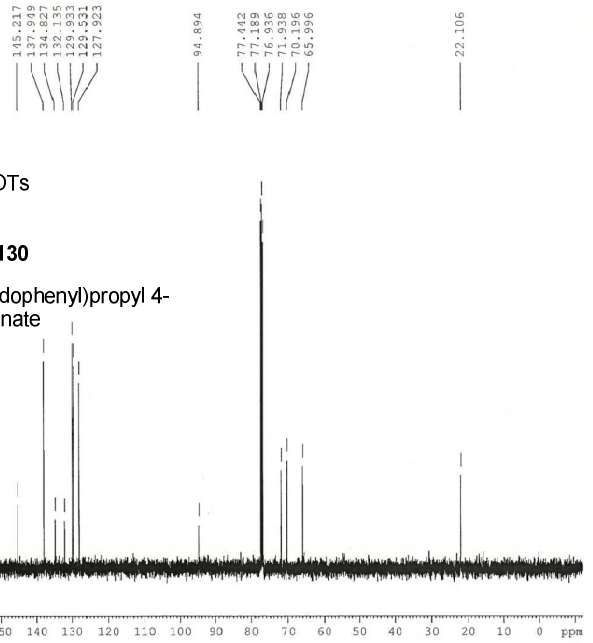
130

(2*R*,3*R*)-3-azido-2-hydroxy-3-(4-iodophenyl)propyl 4-methylbenzenesulfonate




```
Current Data Parameters
NAME                 vb-br-06
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20050202
Time                   10.31
INSTRUM                spect
PROBHD     5 mm Dual 13C/
PULPROG                zg30
TD                    32768
SOLVENT                CDCl3
NS                        16
DS                         0
SWH                7002.801 Hz
FIDRES             0.213709 Hz
AQ                 2.3396852 sec
RG                       256
DW                  71.400 usec
DE                   4.50 usec
TE                   300.0 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                    13.00 usec
PL1                    3.00 dB
SFO1          500.1330008 MHz

F2 - Processing parameters
SI                        32768
SF                500.1300000 MHz
WDW                        EM
SSB                         0
LB                     0.30 Hz
GB                          0
PC                       1.00
```

CARBON

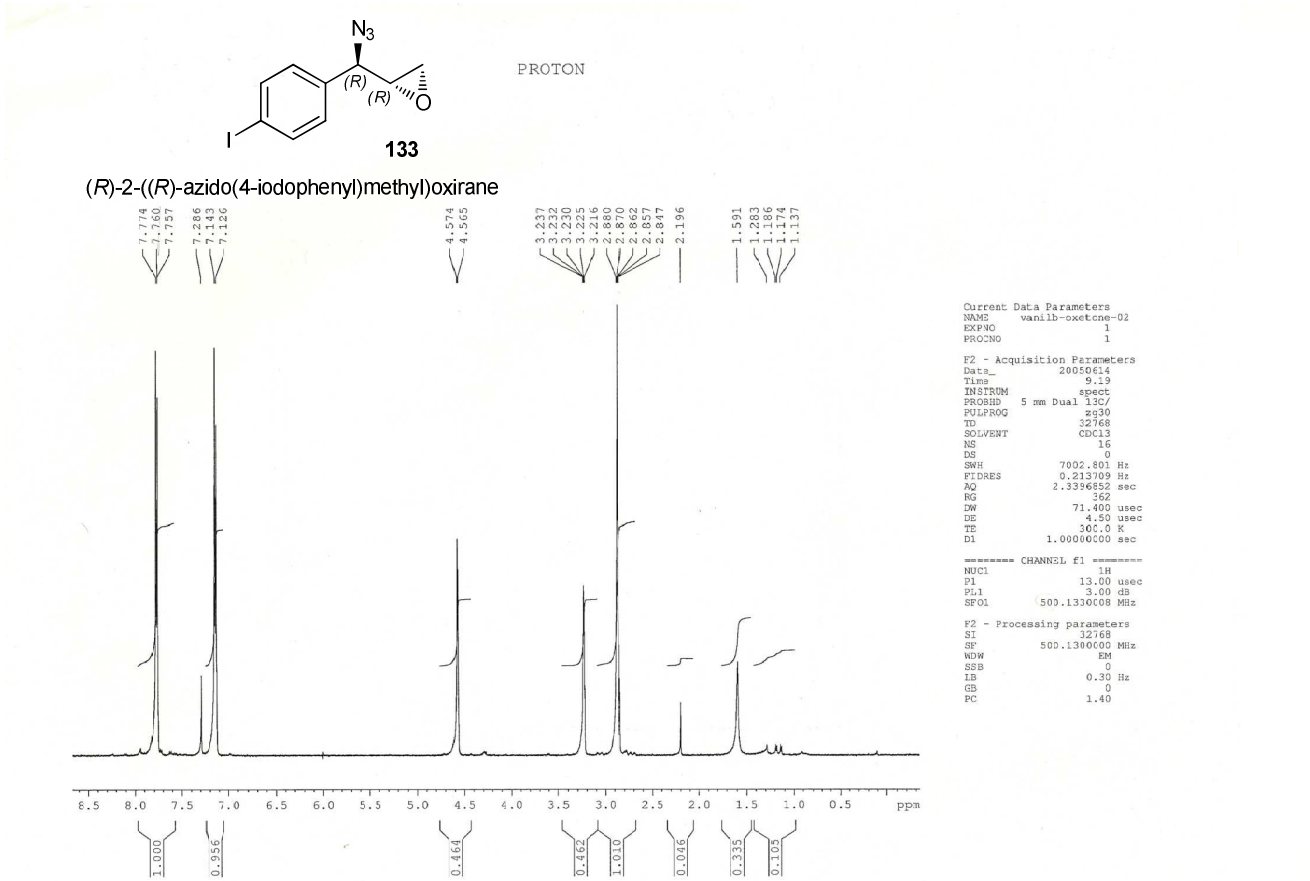


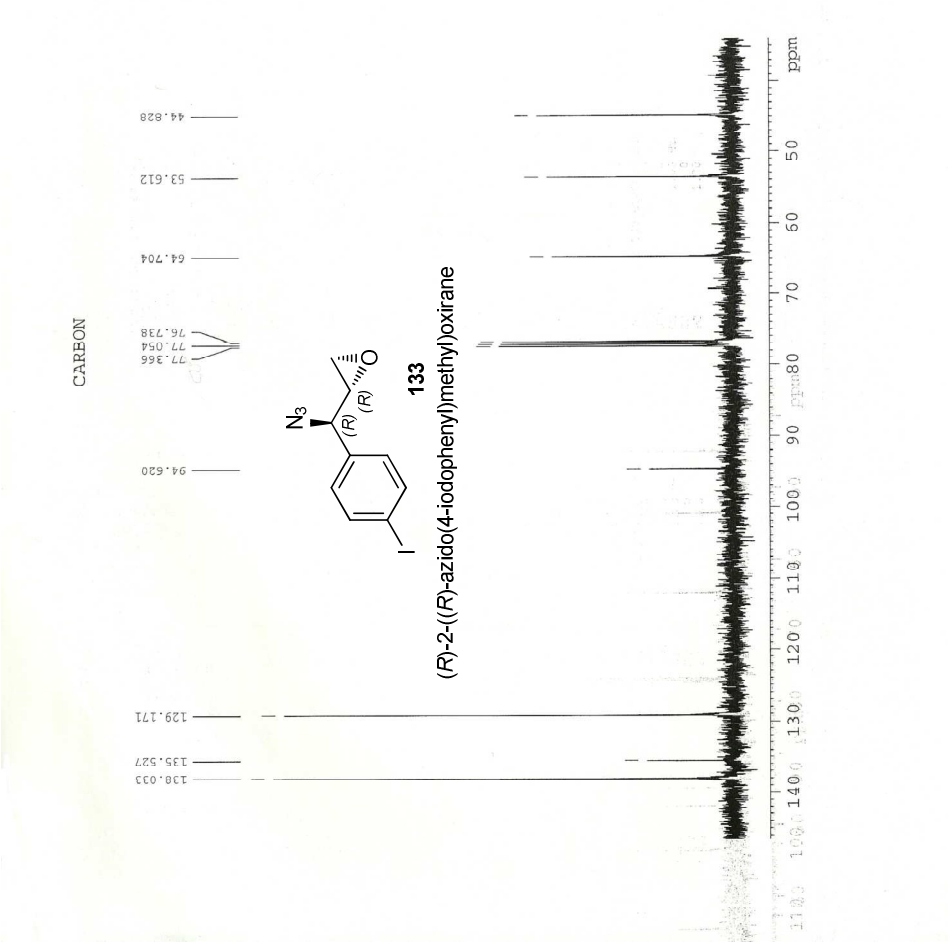
130

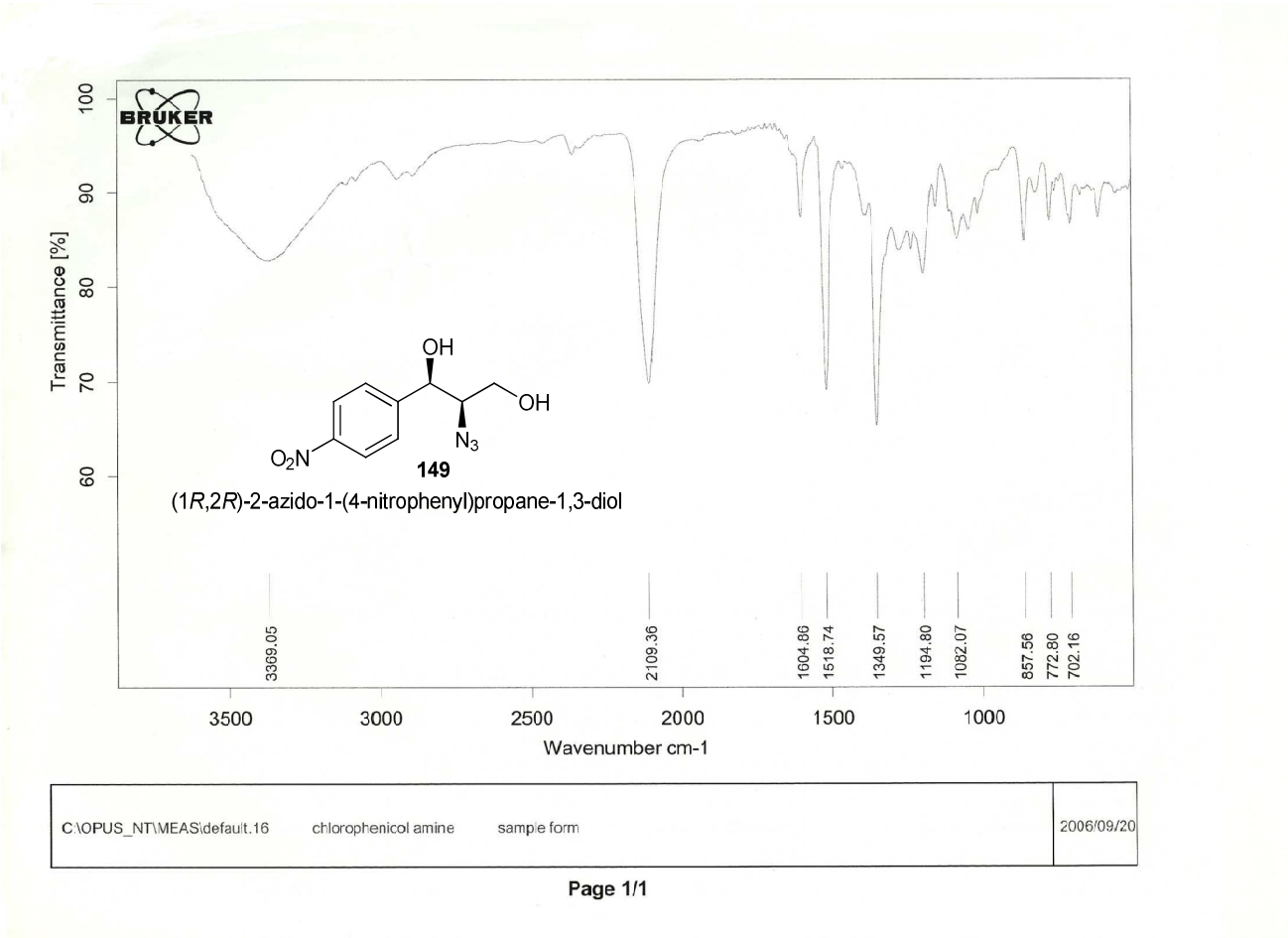
(2*R*,3*R*)-3-azido-2-hydroxy-3-(4-iodophenyl)propyl 4-methylbenzenesulfonate

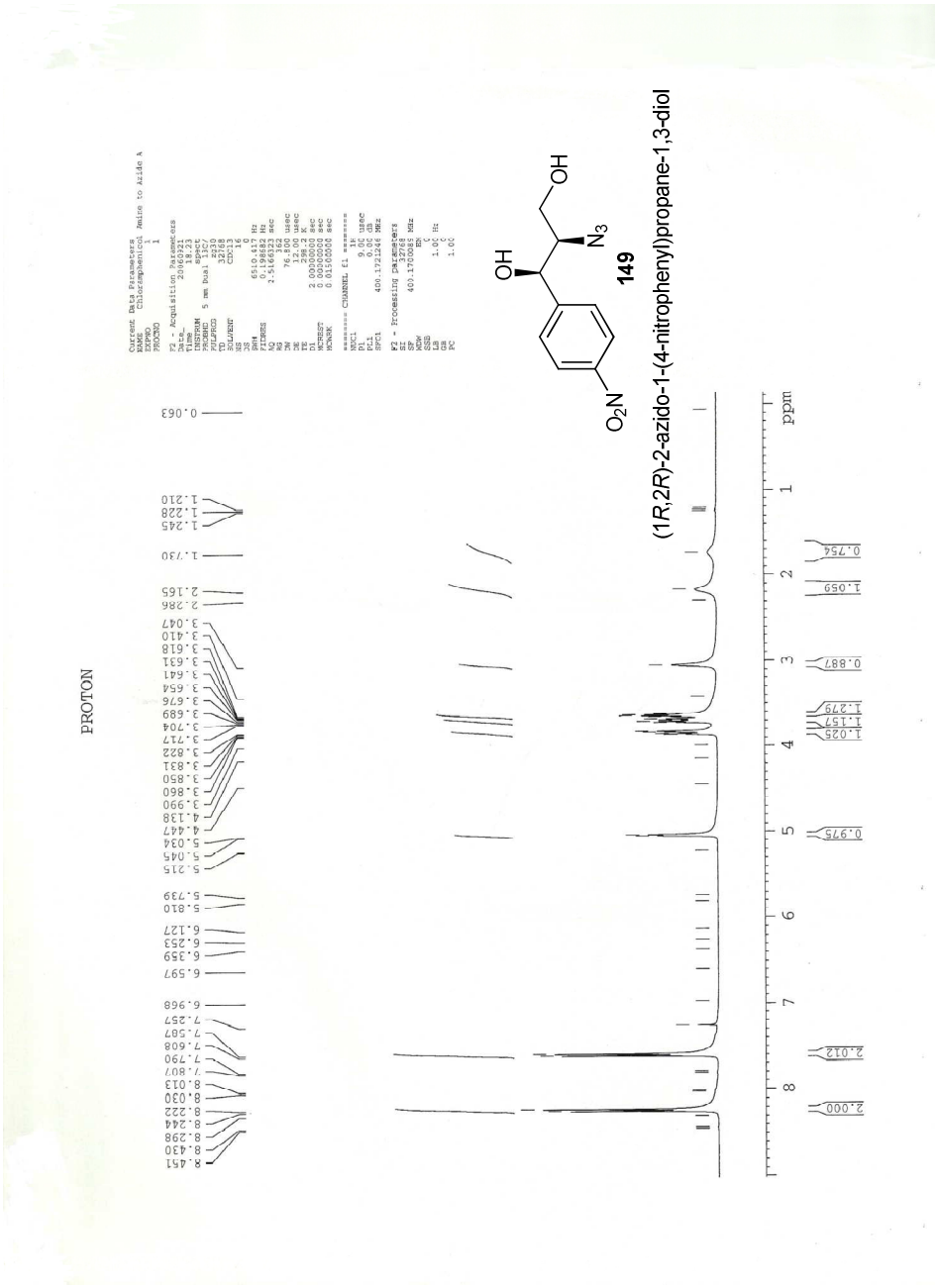
```
Current Data Parameters
NAME                  vb-br-06
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20050202
Time                    10.46
INSTRUM                 spect
PROBHD   5 mm Dual 13C/
PULPROG                 zgdc30
TD                       65536
SOLVENT                  CDCl3
NS                         193
DS                           4
SWH                29498.525 Hz
FIDRES             0.450112 Hz
AQ                 1.1108851 sec
RG                   11585.2
DW                  16.950 usec
DE                   6.00 usec
TE                  300.0 K
D1                3.00000000 sec
d11               0.03000000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                       8.00 usec
PL1                      3.00 dB
SFO1           125.7709936 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  100.00 usec
PL2                      3.00 dB
PL12                    22.00 dB
SFO2           500.1320005 MHz

F2 - Processing parameters
SI                       32768
SF             125.7577890 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
```

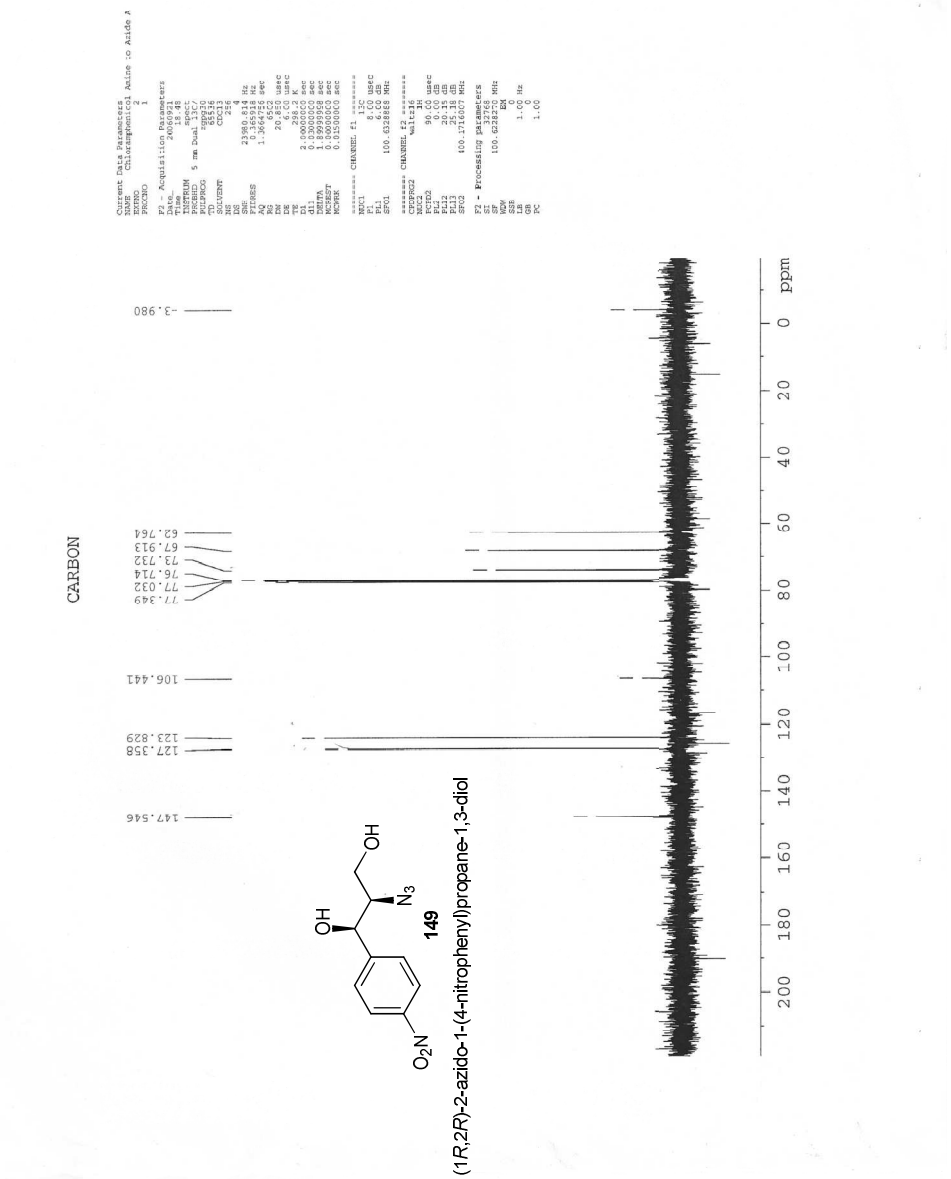
BRUKER
Transmittance [%]
0
20
40
60
80
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
3853.57
3735.24
3675.65
3649.19
2994.34
2360.76
2103.39
1699.35
1587.55
1541.36
1507.64
1486.13
1398.59
1296.19
1252.55
1134.54
1061.62
1007.09
970.98
864.03
837.13
719.12
452.11
419.06
410.03
133
(R)-2-((R)-azido(4-iodophenyl)methyl)oxirane
C:\OPUS_NT\MEAS\azide oxetane solid 1
azide oxetane solid
sample form
2005/07/15
Page 1/1


N3
(R)
(R)
O
I
133
(R)-2-((R)-azido(4-iodophenyl)methyl)oxirane
PROTON
7.774
7.760
7.757
7.286
7.143
7.126
4.574
4.565
3.237
3.232
3.230
3.225
3.216
2.880
2.870
2.862
2.857
2.847
2.196
1.591
1.283
1.186
1.174
1.137
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.000
0.956
0.464
0.462
1.010
0.046
0.335
0.105
Current Data Parameters
NAME vanilb-oxetcne-02
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050614
Time 9.19
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 7002.801 Hz
FIDRES 0.213709 Hz
AQ 2.3396852 sec
RG 262
DW 71.400 usec
DE 4.50 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 13.00 usec
PL1 3.00 dB
SFO1 500.1330008 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

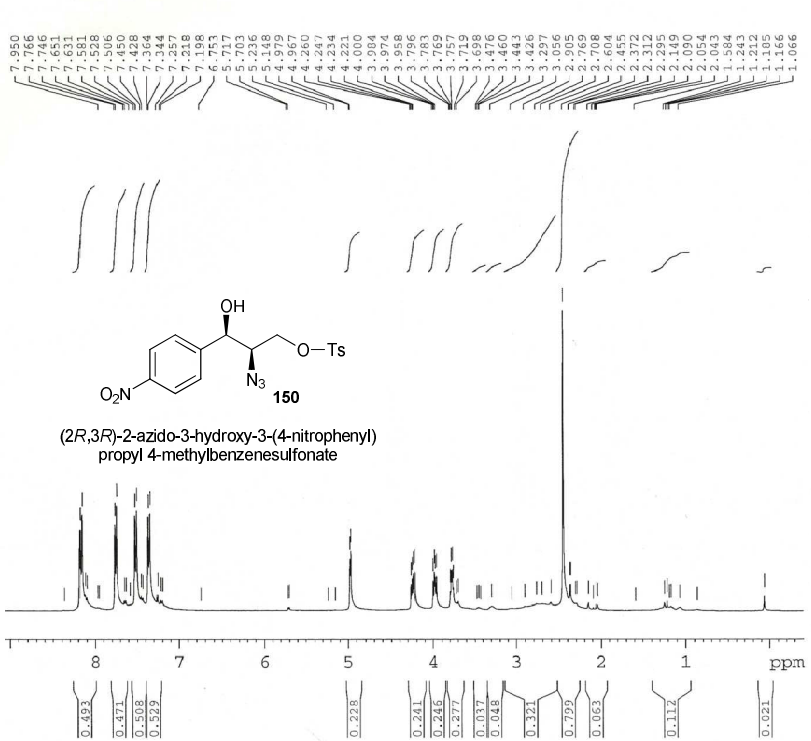

CARBON
Current Data Parameters
NAME vb-br-07
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050225
Time 13.49
INSTRUM spect
PROBHD 5 mm Dual 13
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 256
DS 2
SWH 23148.148 Hz
FIDRES 0.353213 Hz
AQ 1.4156213 sec
RG 11585.2
DW 21.600 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.50 usec
PL1 0.00 dB
SF01 100.6238364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0.00 dB
PL12 18.00 dB
SF02 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
77.366
77.054
76.738
64.704
53.612
44.828
94.620
129.171
135.527
130.033
ppm
133
(R)-2-((R)-azido(4-iodophenyl)methyl)oxirane


BRUKER
Transmittance [%]
100
90
80
70
60
OH
OH
N3
O2N
149
(1R,2R)-2-azido-1-(4-nitrophenyl)propane-1,3-diol
3369.05
2109.36
1604.86
1518.74
1349.57
1194.80
1082.07
857.56
772.80
702.16
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
C:\OPUS_NT\MEAS\default.16
chlorophenicol amine
sample form
2006/09/20
Page 1/1

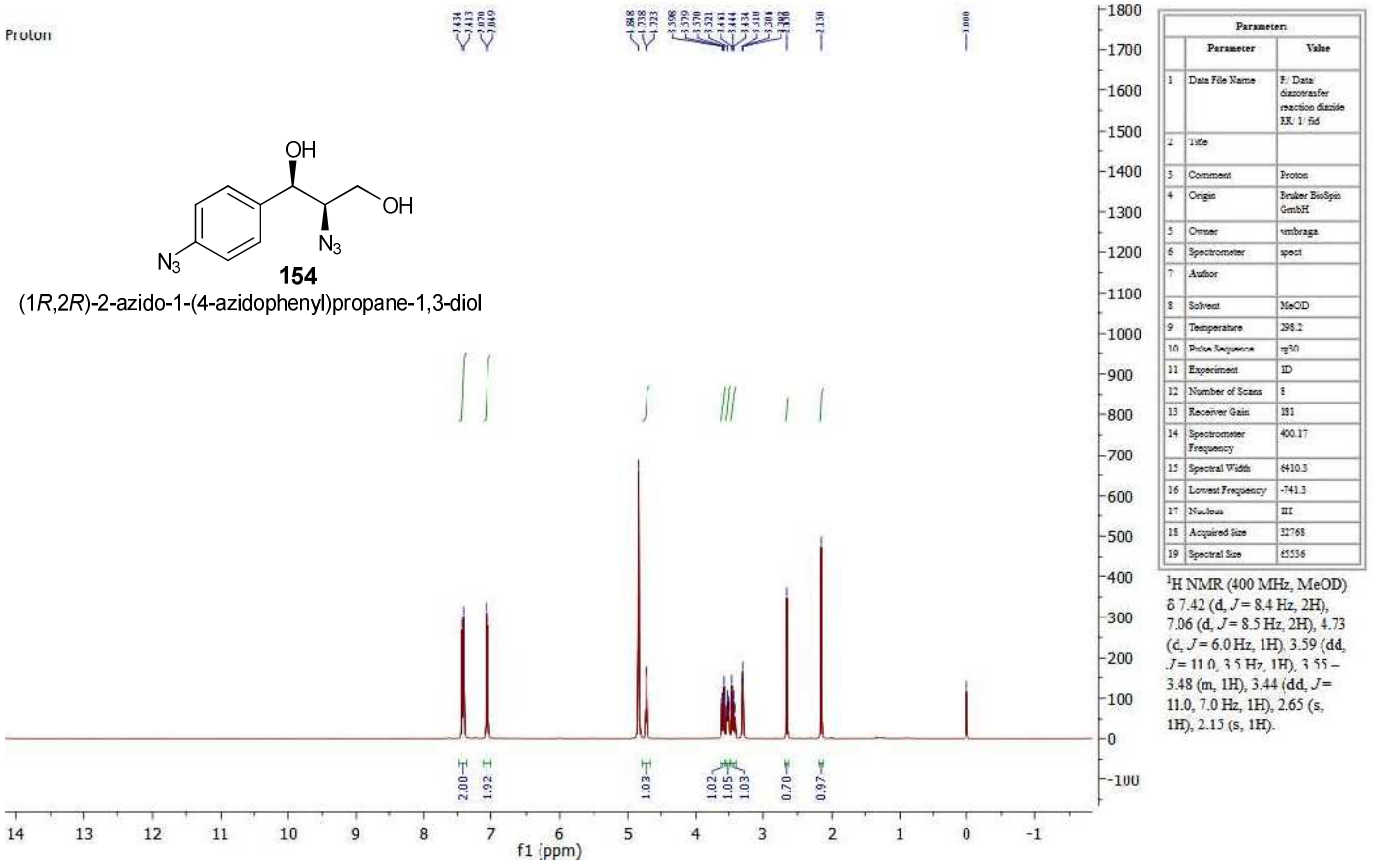

PROTON
(1R,2R)-2-azido-1-(4-nitrophenyl)propane-1,3-diol
149
OH
OH
N3
O2N
ppm


CARBON
147.546
127.358
123.829
106.441
77.349
77.032
76.714
73.732
67.913
62.764
-3.980
ppm
0
20
40
60
80
100
120
140
160
180
200
OH
OH
N3
O2N
149
(1R,2R)-2-azido-1-(4-nitrophenyl)propane-1,3-diol

PROTON

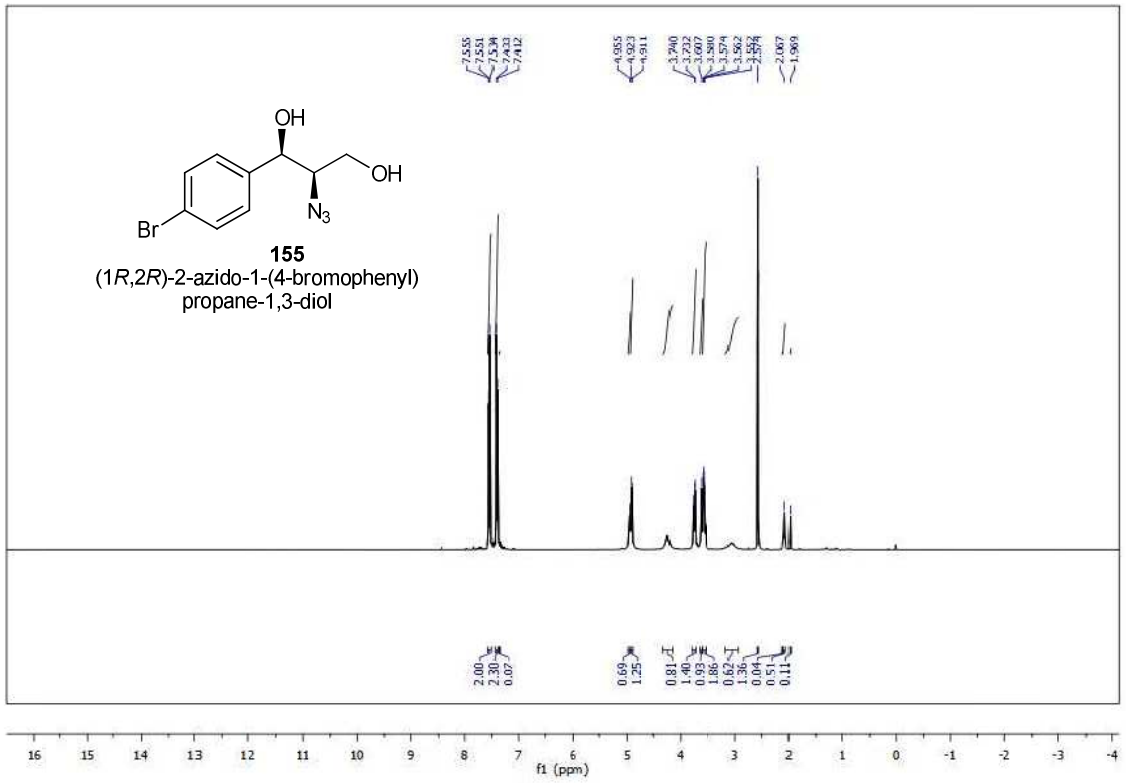



```
Current Data Parameters
NAME       Tosylation 38
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20060926
Time              17.35
INSTRUM           spect
PROBHD   5 mm Dual 13C/
PULPROG           zg30
TD               32768
SOLVENT          CDCl3
NS                  32
DS                   0
SWH           6510.417 Hz
FIDRES        0.198682 Hz
AQ            2.5166323 sec
RG                 181
DW               76.800 usec
DE               12.00 usec
TE              298.2 K
D1            2.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                1H
P1                9.00 usec
PL1               0.00 dB
SF01        400.1721246 MHz

F2 - Processing parameters
SI               32768
SF          400.1700089 MHz
WDW                 EM
SSB                  0
LB                1.00 Hz
GB                   0
PC                1.00
```



Parameters		
	Parameter	Value
1	Data File Name	F:\Data\diazotransfer reaction dioxide HK 1\fid
2	Title	
3	Comment	Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Spectrometer	spect
7	Author	
8	Solvent	MeOD
9	Temperature	298.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	8
13	Receiver Gain	181
14	Spectrometer Frequency	400.17
15	Spectral Width	6410.3
16	Lowest Frequency	-741.3
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

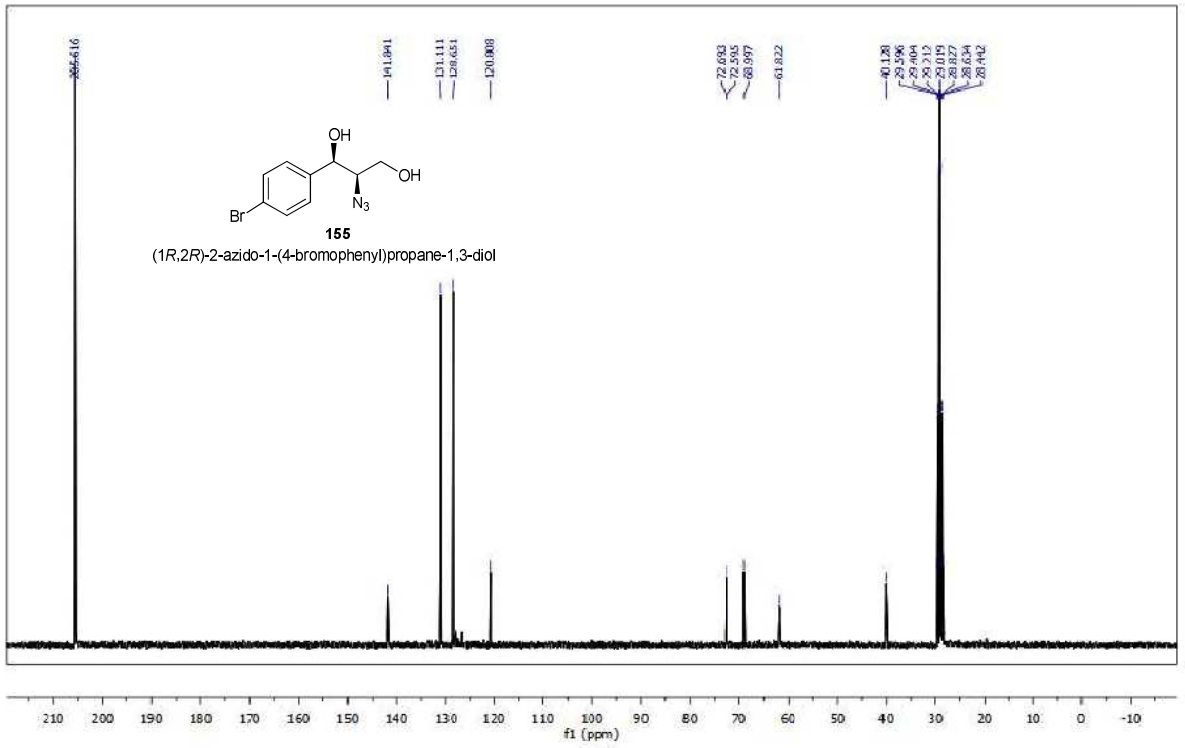
^{1}H NMR (400 MHz, MeOD) δ 7.42 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 4.73 (d, J = 6.0 Hz, 1H), 3.59 (dd, J = 11.0, 3.5 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.44 (dd, J = 11.0, 7.0 Hz, 1H), 2.65 (s, 1H), 2.15 (s, 1H).



155
(1*R*,2*R*)-2-azido-1-(4-bromophenyl) propane-1,3-diol

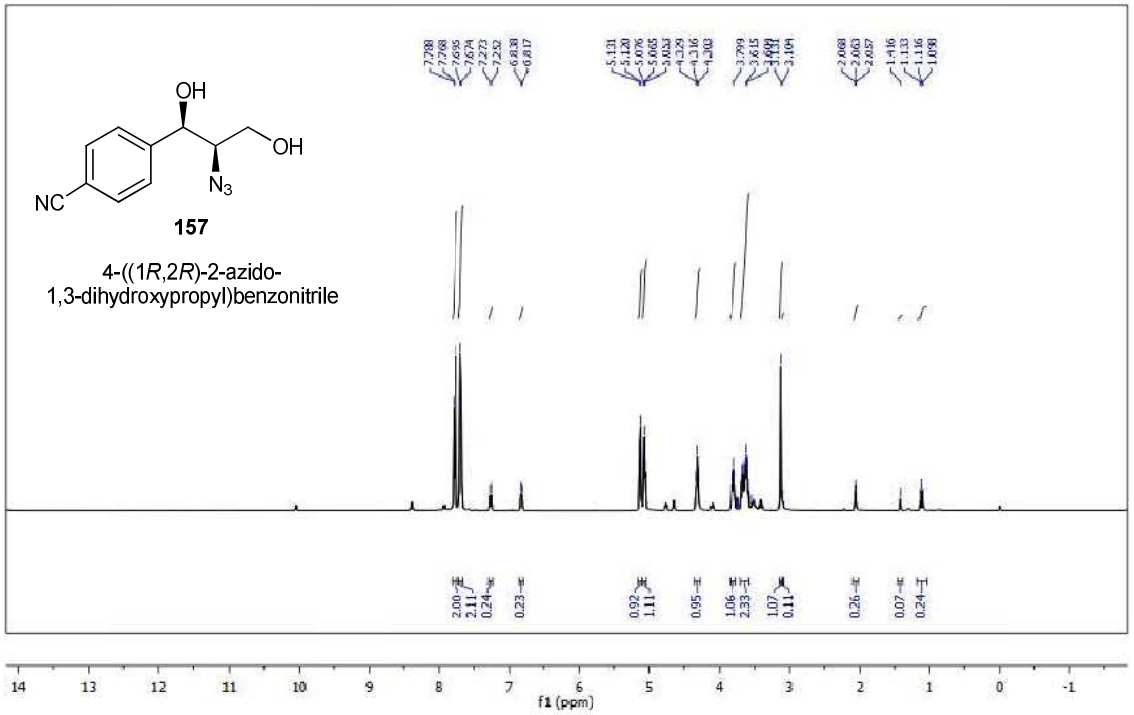
Parameters		
	Parameter	**Value**
1	Data File Name	E:\ sandmeyer bromination\ 1\ pdata\ 1\ 1r
2	Title	PROTON
3	Temperature	
4	Pulse Sequence	Unknown
5	Experiment	1D
6	Number of Scans	nan
7	Spectrometer Frequency	400.13
8	Spectral Width	8250.8
9	Lowest Frequency	-1654.4
10	Nucleus	
11	Acquired Size	
12	Spectral Size	32768

H NMR (400 MHz, acetone) δ 7.58 – 7.51 (m), 7.42 (d, *J* = 8.4 Hz), 4.92 (d, *J* = 4.4 Hz), 4.24 (s), 3.75 (dd, *J* = 10.7, 3.3 Hz), 3.62 (d, *J* = 6.8 Hz), 3.57 (dd, *J* = 7.9, 3.2 Hz), 3.06 (s), 2.57 (s).



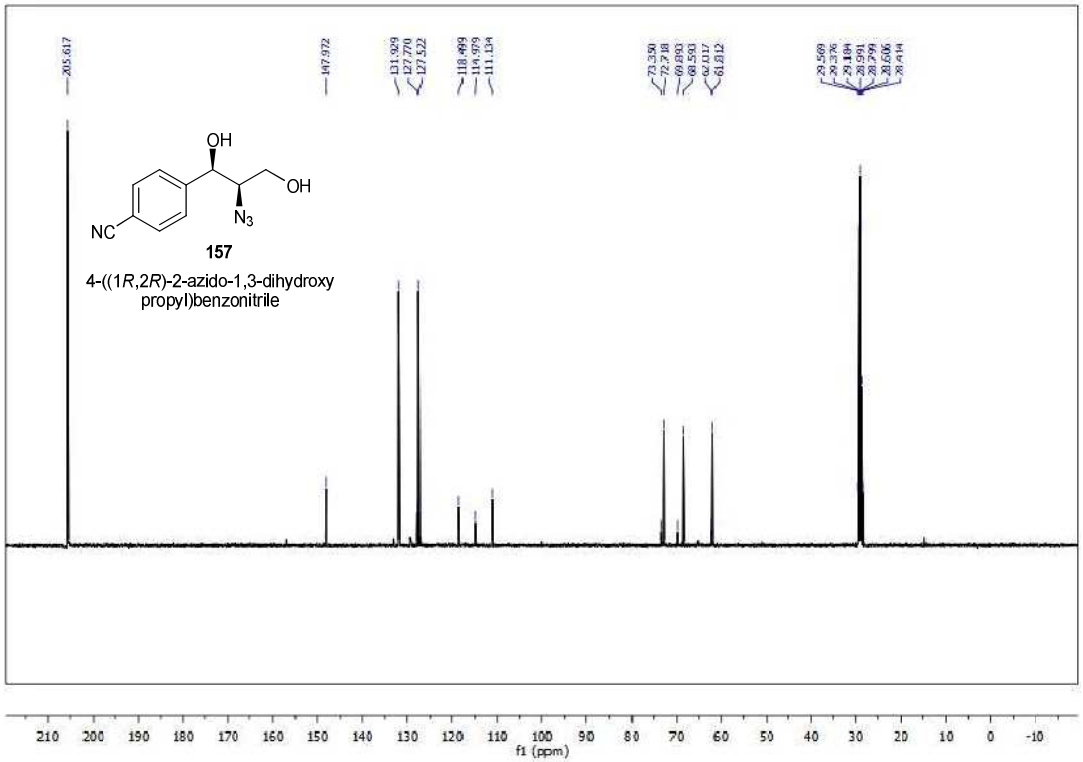
Parameters		
	Parameter	Value
1	Data File Name	E:\sandmeyer bromination\2\fid
2	Title	CARBON
3	Temperature	301.2
4	Pulse Sequence	ZGPG30
5	Experiment	1D
6	Number of Scans	700
7	Spectrometer Frequency	100.62
8	Spectral Width	24038.5
9	Lowest Frequency	-1956.2
10	Nucleus	
11	Acquired Size	
12	Spectral Size	65536

13C NMR (101 MHz, acetone) δ 205.62, 141.84, 131.11, 128.65, 120.81, 72.69, 72.59, 69.00, 61.82, 40.13, 29.60, 29.40, 29.21, 29.02, 28.83, 28.63, 28.44.



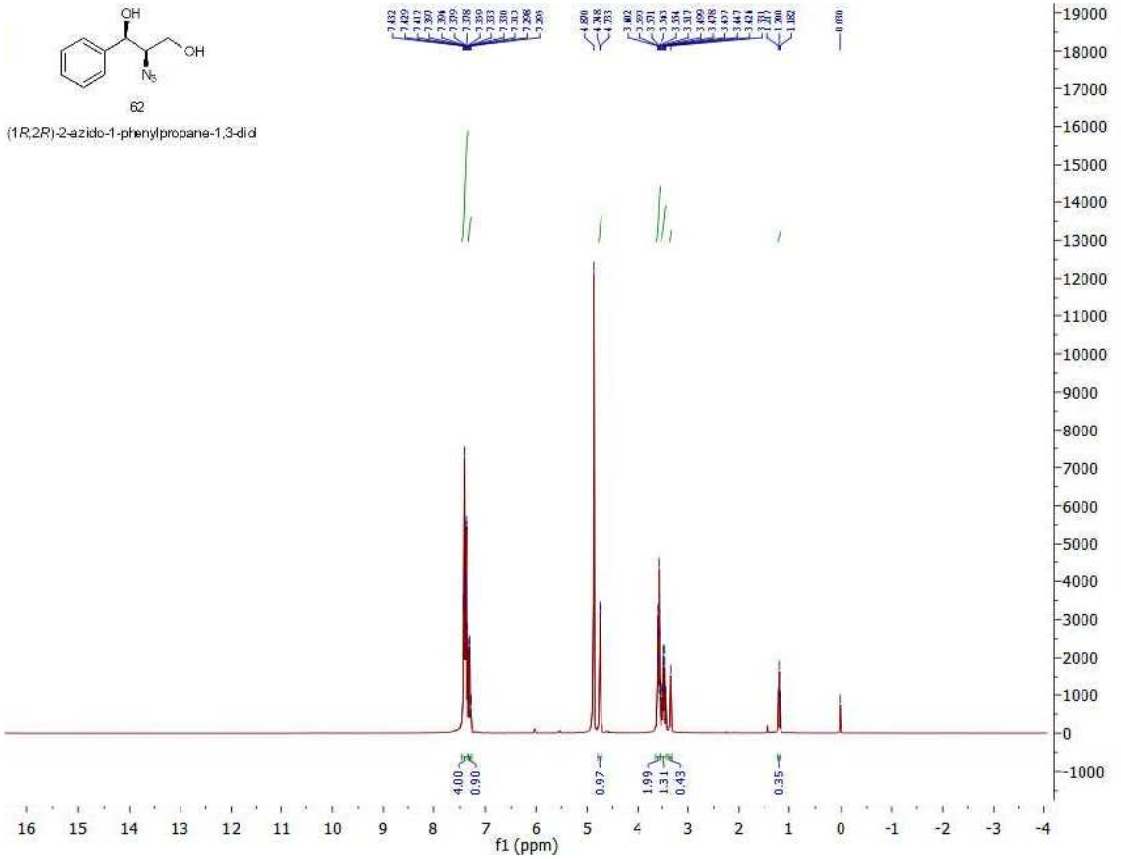
Parameters		
	Parameter	Value
1	Data File Name	E:\ Sandmeyer Cyanation\ 1\ fid
2	Title	Proton
3	Temperature	296.9
4	Pulse Sequence	ZG30
5	Experiment	1D
6	Number of Scans	8
7	Spectrometer Frequency	400.17
8	Spectral Width	6410.3
9	Lowest Frequency	-733.9
10	Nucleus	
11	Acquired Size	
12	Spectral Size	65536

1H NMR (400 MHz,) δ 7.78 (d, J = 8.3 Hz), 7.68 (d, J = 8.2 Hz), 5.13 (d, J = 4.7 Hz), 3.85 – 3.78 (m), 3.63 (ddt, J = 11.0, 6.7, 5.5 Hz), 3.13 (s).



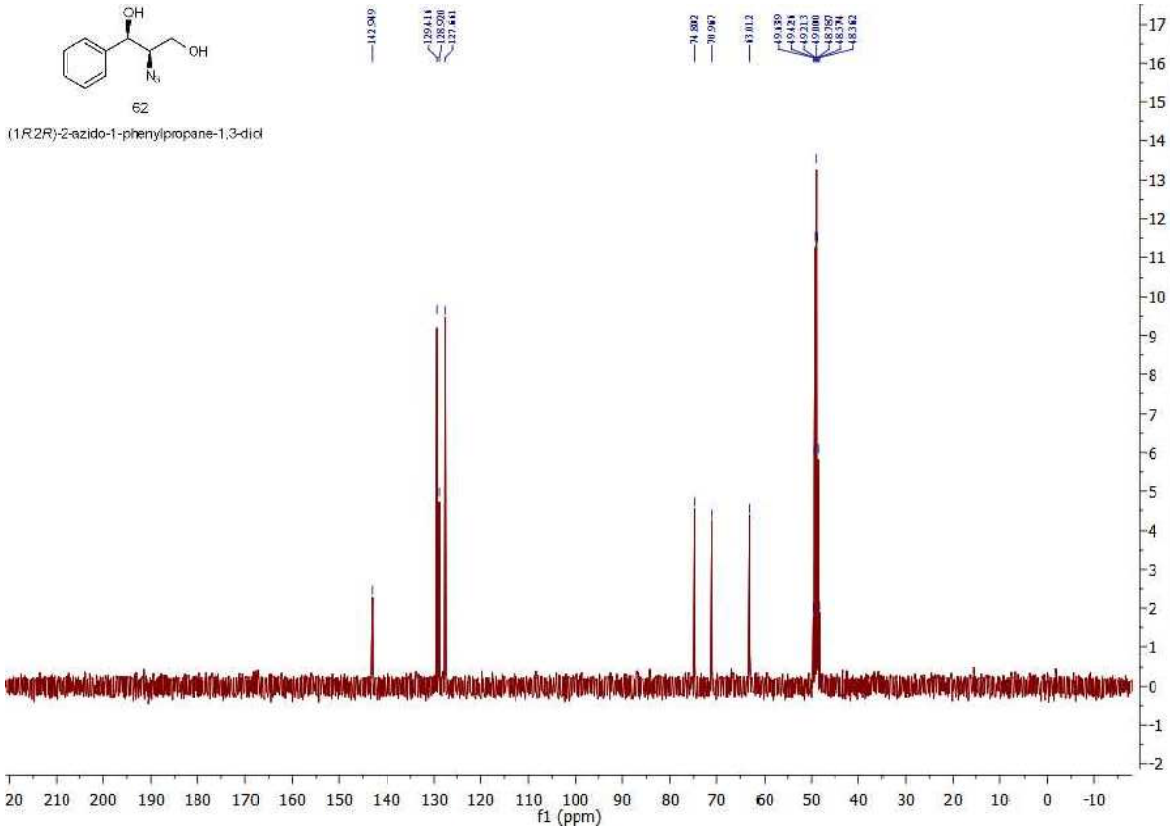
Parameters:		
	Parameter	Value
1	Data File Name	E:\ cyanation sandmeyer\ cyanation sandmeyer\ 1\ fid
2	Title	CARBON
3	Temperature	303.2
4	Pulse Sequence	ZGPG30
5	Experiment	1D
6	Number of Scans	1000
7	Spectrometer Frequency	100.62
8	Spectral Width	24038.5
9	Lowest Frequency	-1956.2
10	Nucleus	
11	Acquired Size	
12	Spectral Size	65536

13C NMR (101 MHz,) δ 205.62, 147.97, 131.93, 127.77, 127.52, 118.50, 114.98, 111.13, 73.35, 72.72, 69.89, 68.59, 62.02, 61.81, 29.57, 29.38, 29.18, 28.99, 28.80, 28.61, 28.41.



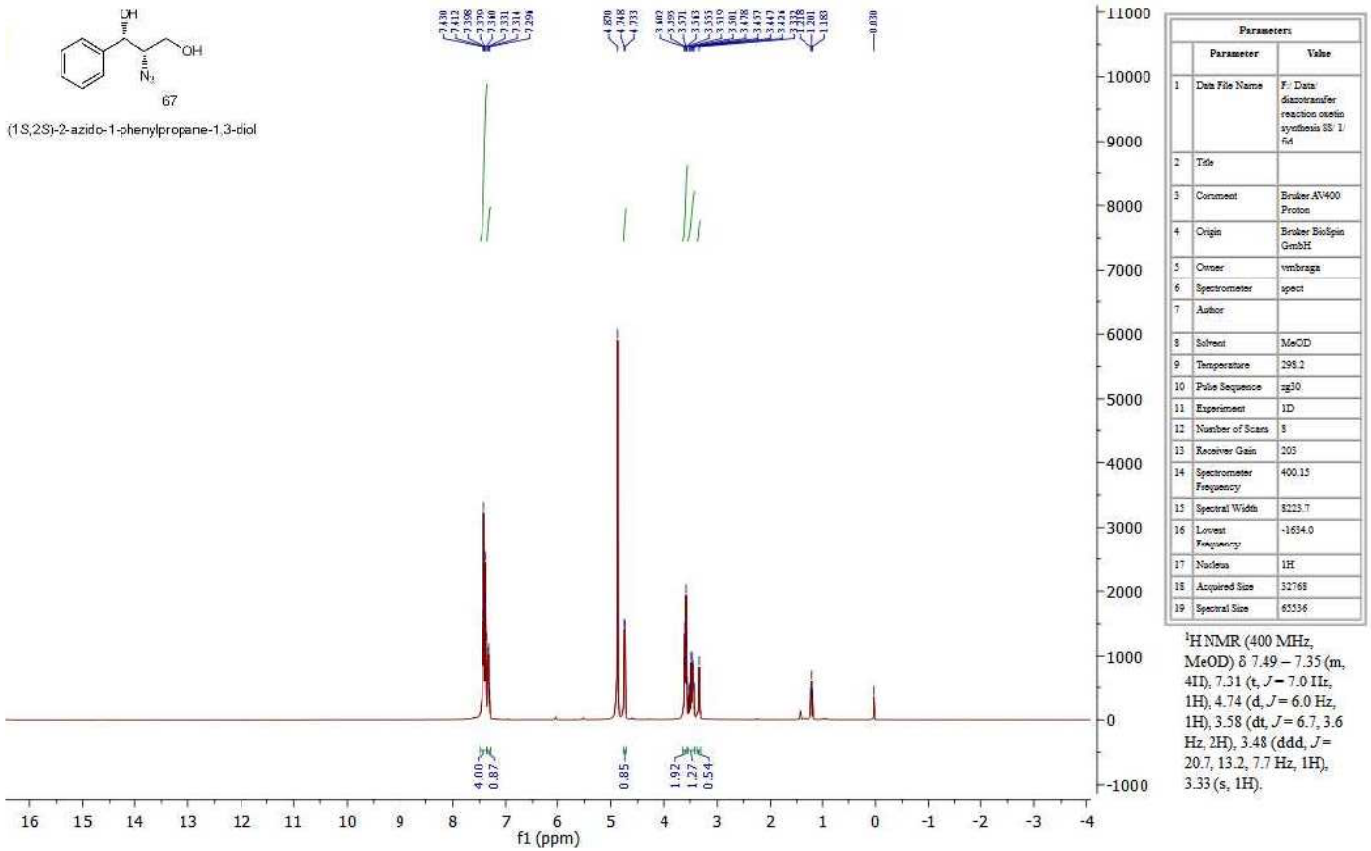
Parameters		
	Parameter	Value
1	Data File Name	F:\Data\ diazotransfer reaction\ouretin synthesis RR\ 1\ fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrbraga
6	Spectrometer	spect
7	Author	
8	Solvent	MeOD
9	Temperature	298.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	16
13	Receiver Gain	181
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1634.4
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

^{1}H NMR (400 MHz, MeOD) δ 7.40 (**ddd**, J = 14.5, 7.9, 4.2 Hz, 4H), 7.35 – 7.28 (**m**, 1H), 4.74 (**d**, J = 6.0 Hz, 1H), 3.64 – 3.54 (**m**, 2H), 3.48 (**ddd**, J = 20.8, 13.2, 7.7 Hz, 1H), 3.33 (**s**, 1H), 1.20 (**t**, J = 7.0 Hz, 1H).



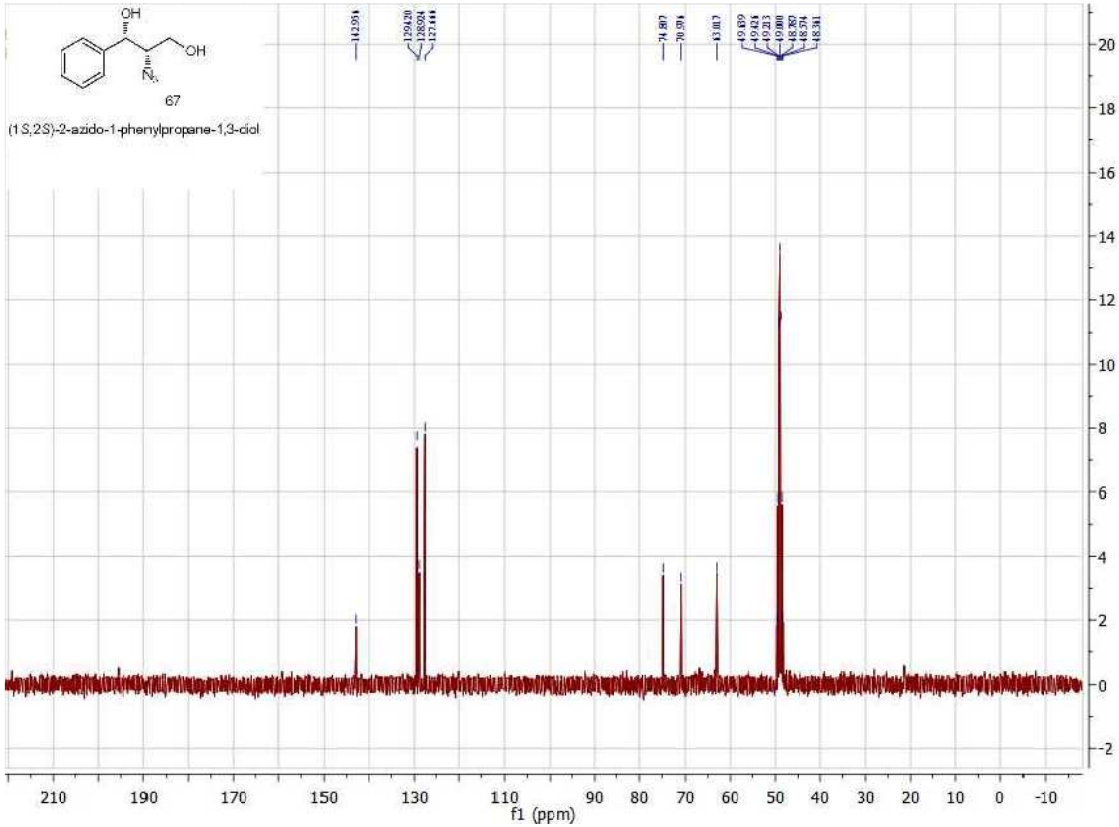
Parameters		
	Parameter	Value
1	Data File Name	F:\Data\diazotransfer reaction orotin synthesis RR_2\1\fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vrrbraga
6	Spectrometer	spect
7	Author	
8	Solvent	MeOD
9	Temperature	298.2
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	100
13	Receiver Gain	32800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1820.0
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

^{13}C NMR (101 MHz, MeOD) δ 142.95, 129.42, 128.92, 127.66, 74.80, 70.97, 63.01, 49.64, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36.



Parameters		
	Parameter	Value
1	Data File Name	F:\ Data\ diazotransfer reaction onetin synthesis SS\ 1\ fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	MeOD
9	Temperature	298.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	8
13	Receiver Gain	203
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1634.0
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

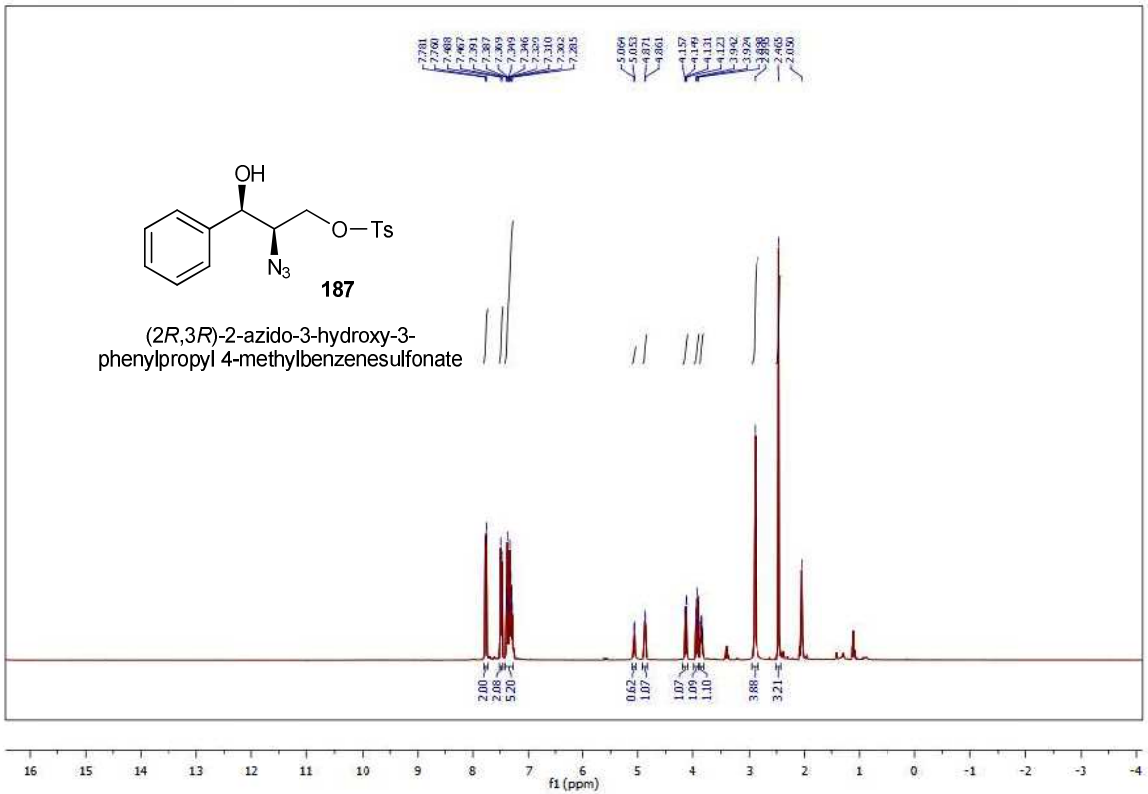
^{1}H NMR (400 MHz, MeOD) δ 7.49 – 7.35 (m, 4H), 7.31 (t, J = 7.0 Hz, 1H), 4.74 (d, J = 6.0 Hz, 1H), 3.58 (dt, J = 6.7, 3.6 Hz, 2H), 3.48 (ddd, J = 20.7, 13.2, 7.7 Hz, 1H), 3.33 (s, 1H).



Parameters		
	Parameter	Value
1	Data File Name	F:\ Data\ diazotransfer reaction oxetin synthesis SS\ 2\ 5d
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	apect
7	Author	
8	Solvent	MeOD
9	Temperature	298.2
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	100
13	Receiver Gain	31800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1819.2
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

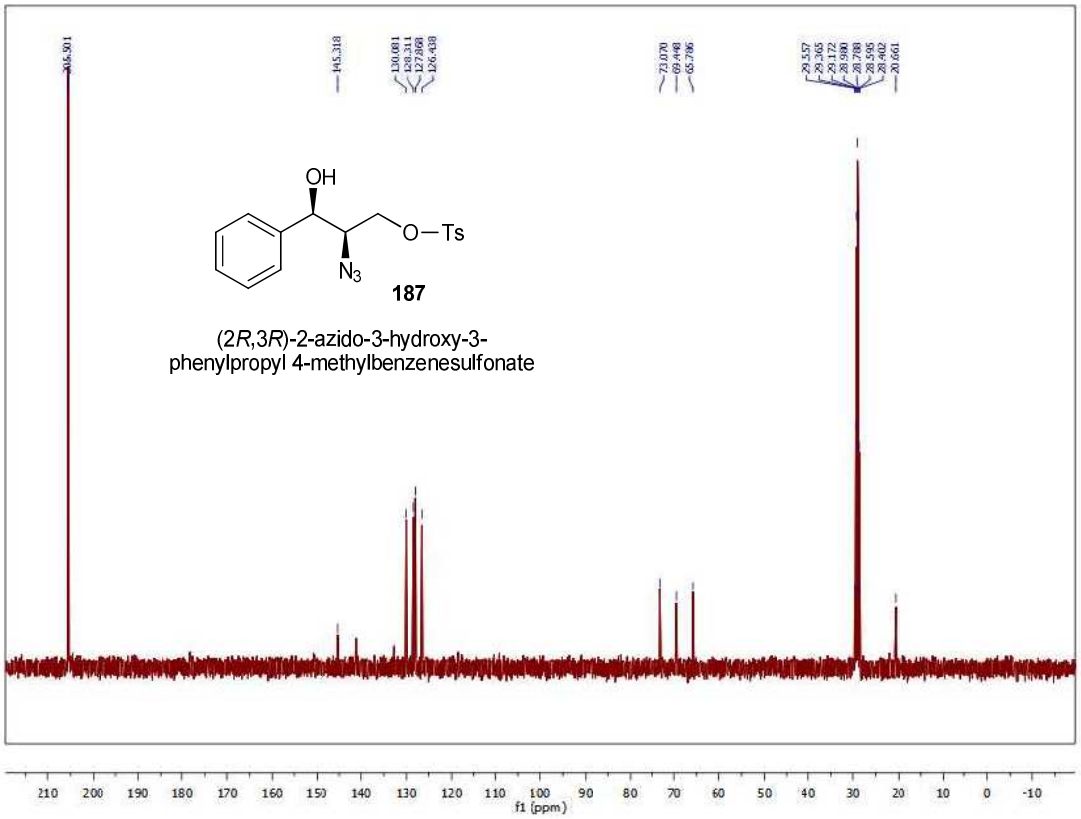
^{13}C NMR (101 MHz, MeOD) δ 142.96, 129.42, 128.92, 127.67, 74.81, 70.98, 63.02, 49.64, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36.

Transmittance [%]
92
94
96
98
100
102
104
Wavenumber cm-1
3500
3000
2500
2000
1500
1000
3522.42
2113.47
1598.98
1361.00
1191.08
1176.33
1097.29
979.32
815.09
764.77
703.61
665.12
OH
N3
O—Ts
187
(2R,3R)-2-azido-3-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate
BRUKER
C:\OPUS_NT\MEAS\SMC.11
oxetin synthesis tosyl RR
sample form
2009/08/04
Page 1/1



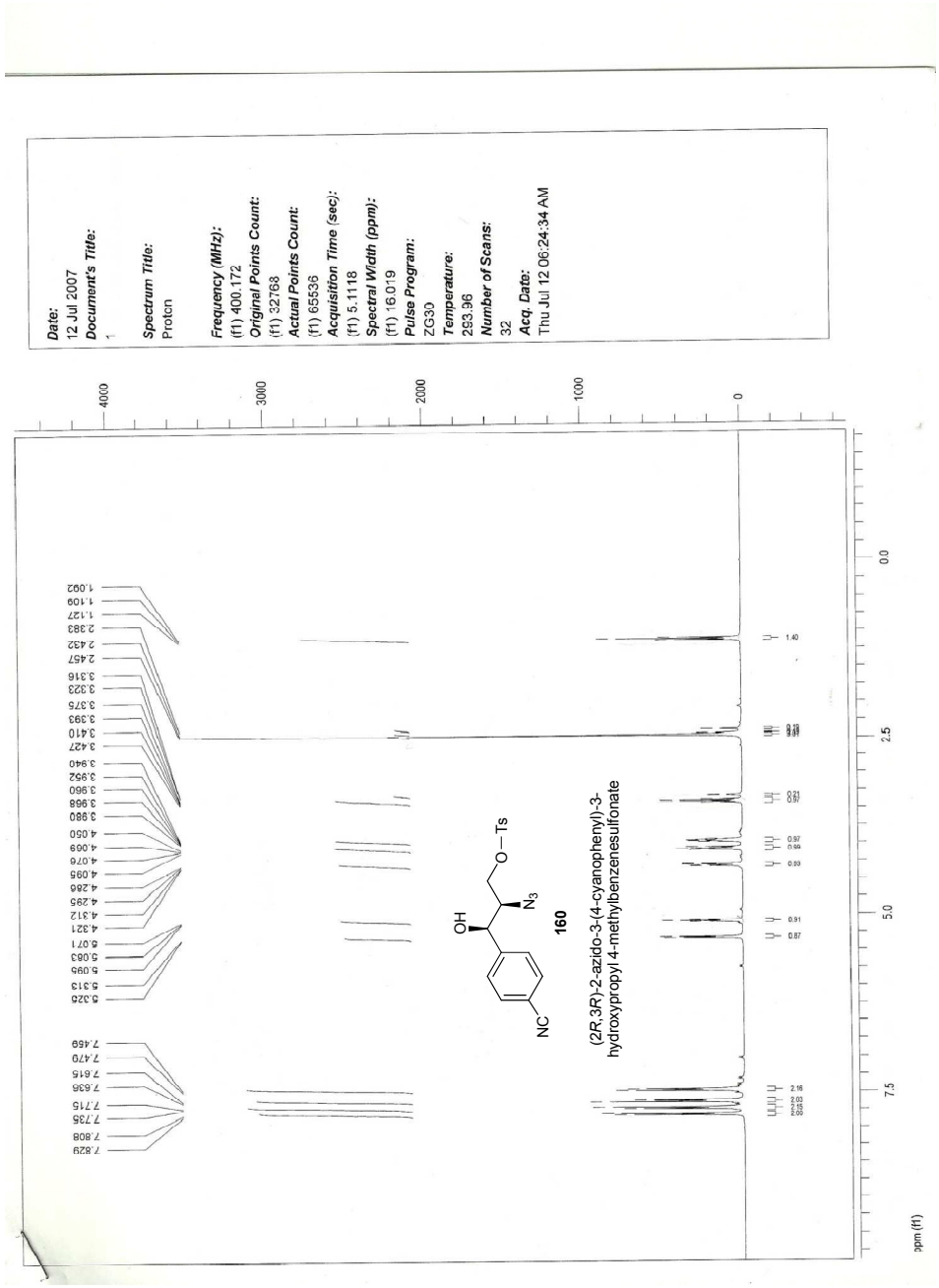
Parameters		
	Parameter	Value
1	Data File Name	F:\ Data\ cuetin synthesis tosylation 1\ fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	298.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	8
13	Receiver Gain	256
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1644.8
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

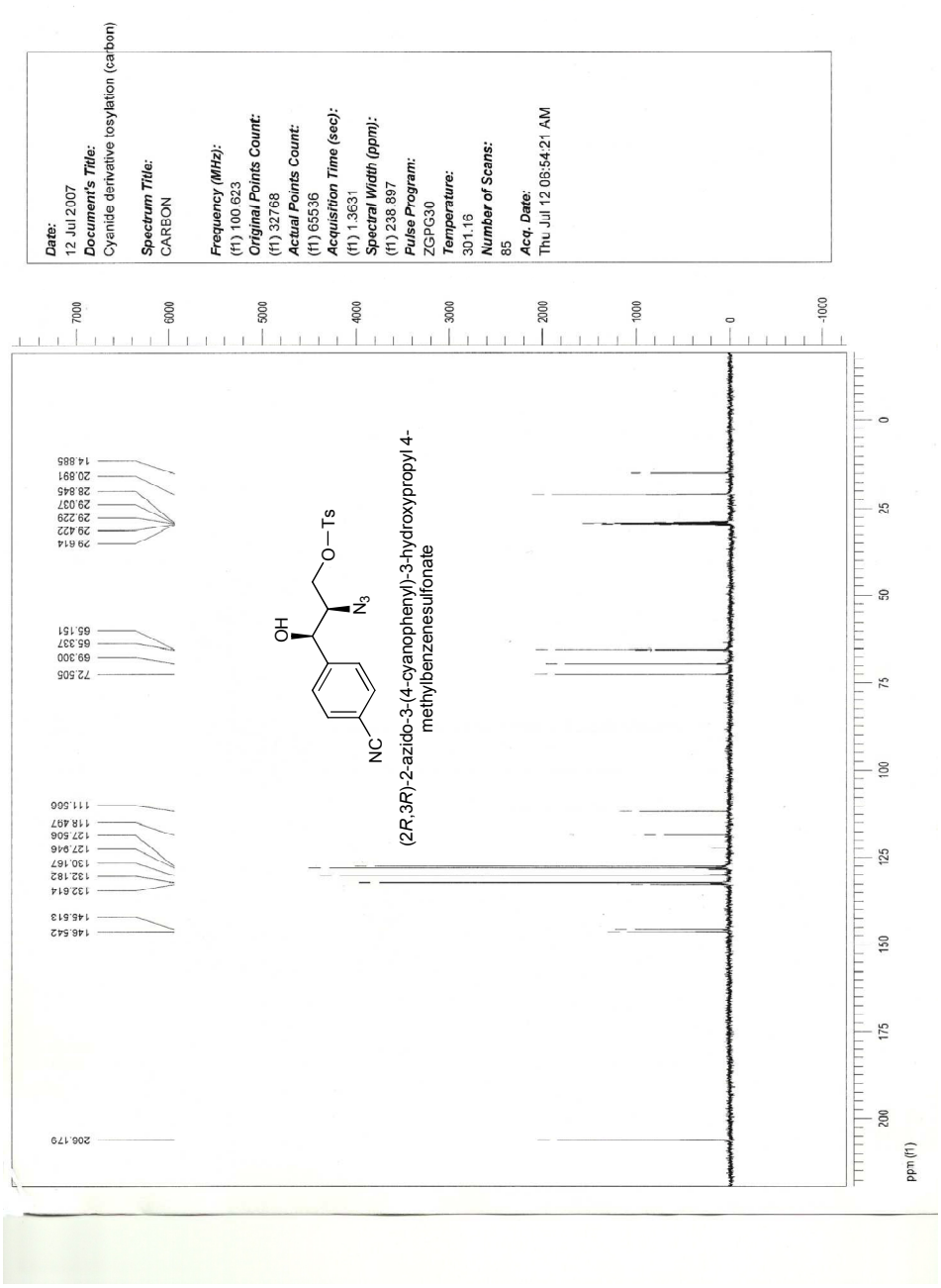
^{1}H NMR (400 MHz, Acetone) δ 7.77 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.41 – 7.27 (m, 5H), 4.87 (d, J = 3.8 Hz, 1H), 4.14 (dd, J = 10.4, 3.2 Hz, 1H), 3.92 (dd, J = 10.4, 7.5 Hz, 1H), 3.89 – 3.81 (m, 1H), 2.46 (s, 3H).

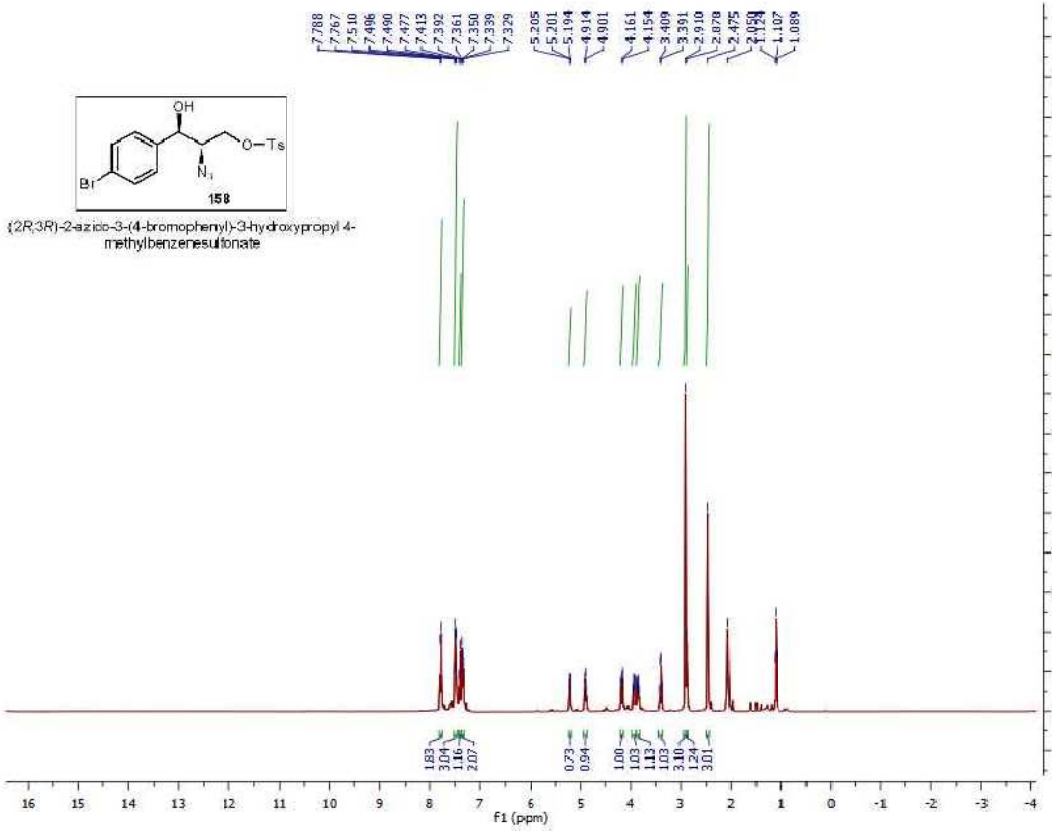


Parameters		
	Parameter	Value
1	Data File Name	F:\ Data\ cretin synthesis tosylation\ 2\ fid
2	Title	
3	Comment	Bruker AV400 Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	294.3
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	80
13	Receiver Gain	32800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1957.9
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

^{13}C NMR (101 MHz, Acetcne) δ 205.50, 145.32, 130.08, 128.31, 127.87, 126.44, 73.07, 69.45, 65.79, 29.56, 29.36, 29.17, 28.98, 28.79, 28.60, 28.40, 20.66.

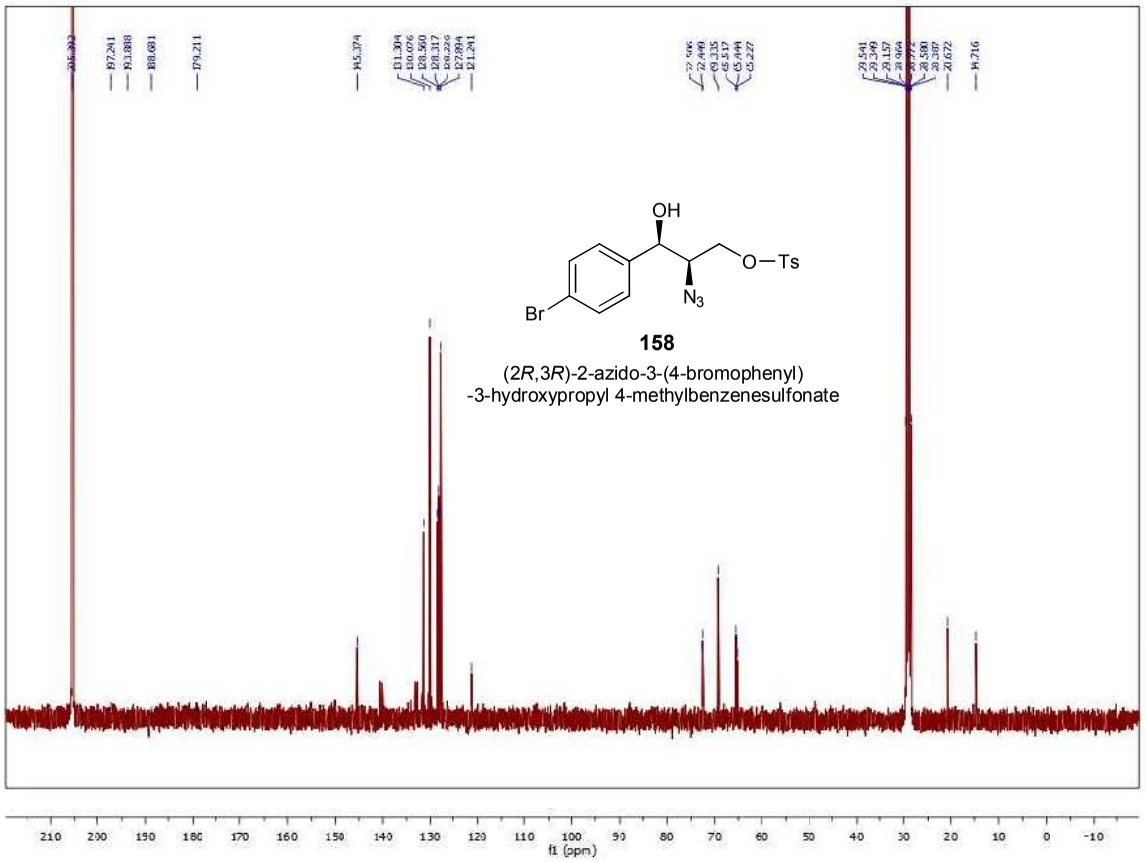

Date:
12 Jul 2007
Document's Title:
1
Spectrum Title:
Protcn
Frequency (MHz):
(f1) 400.172
Original Points Count:
(f1) 32768
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 5.1118
Spectral Width (ppm):
(f1) 16.019
Pulse Program:
ZG30
Temperature:
293.96
Number of Scans:
32
Acq. Date:
Thu Jul 12 06:24:34 AM
4000
3000
2000
1000
0
1.092
1.109
1.127
2.383
2.432
2.457
3.316
3.323
3.375
3.393
3.410
3.427
3.940
3.952
3.960
3.968
3.980
4.050
4.069
4.076
4.095
4.286
4.295
4.312
4.321
5.071
5.063
5.095
5.313
5.325
7.469
7.479
7.615
7.636
7.715
7.735
7.808
7.829
OH
O—Ts
N3
NC
160
(2R,3R)-2-azido-3-(4-cyanophenyl)-3-hydroxypropyl 4-methylbenzenesulfonate
1.40
0.97
0.99
0.89
0.91
0.87
2.16
2.03
2.03
0.0
2.5
5.0
7.5
ppm (f1)


Date:
12 Jul 2007
Document's Title:
Cyanide derivative tosylation (carbon)
Spectrum Title:
CARBON
Frequency (MHz):
(f1) 100.623
Original Points Count:
(f1) 32768
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 1.3631
Spectral Width (ppm):
(f1) 238.897
Pulse Program:
ZGPG30
Temperature:
301.16
Number of Scans:
85
Acq. Date:
Thu Jul 12 08:54:21 AM
OH
O—Ts
N3
NC
(2R,3R)-2-azido-3-(4-cyanophenyl)-3-hydroxypropyl 4-methylbenzenesulfonate
ppm (f1)



Parameters		
	Parameter	Value
1	Data File Name	C:\Users\Vanildo Braga\Documents\My Spectra\Tosylation Bromine\1\fid
2	Title	Bruker AV400 Proton
3	Origin	Bruker BioSpin GmbH
4	Owner	vrnbraga
5	Solvent	Acetone
6	Pulse Sequence	zg30
7	Acquisition Date	2008-09-19T11:23:06
8	Modification Date	
9	Temperature	294.7
10	Number of Scans	16
11	Spectrometer Frequency	400.15
12	Spectral Width	8223.7
13	Lowest Frequency	-1640.8
14	Nucleus	1H
15	Acquired Size	32768
16	Spectral Size	65536

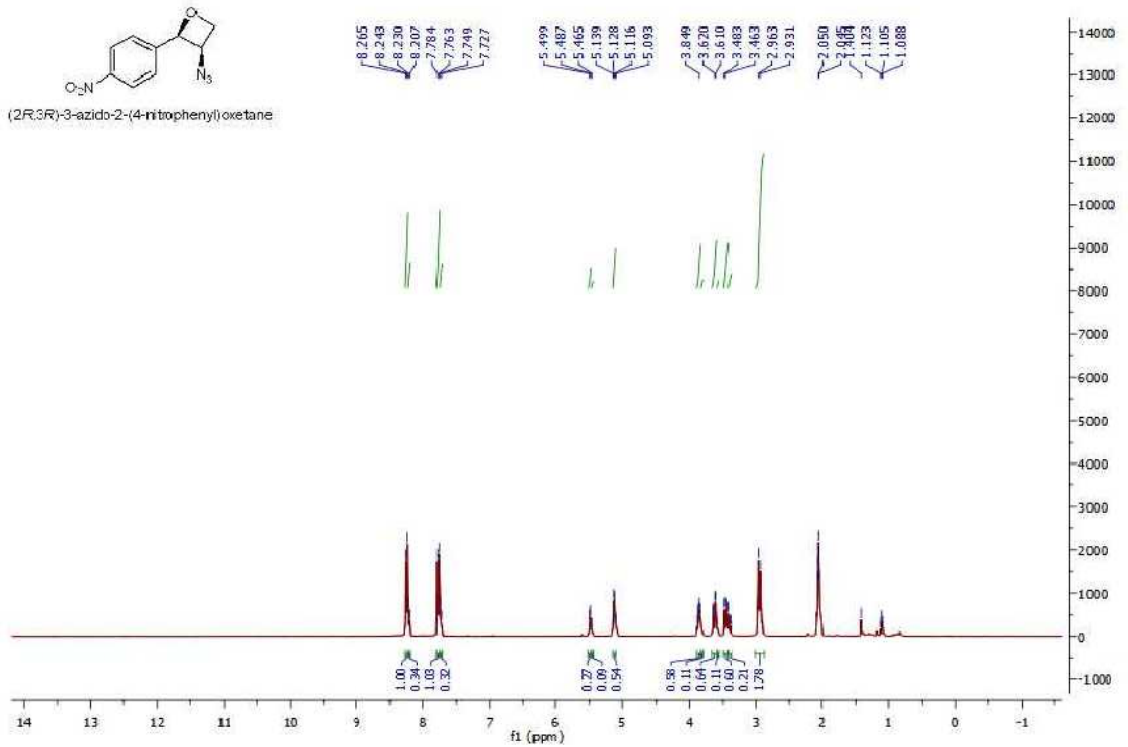
^{1}H NMR (400 MHz, Acetone) δ 7.78 (d, J = 8.2 Hz, 1H), 7.49 (dd, J = 8.1, 5.3 Hz, 2H), 7.40 (d, J = 8.5 Hz, 1H), 7.34 (dd, J = 8.4, 4.3 Hz, 1H), 5.20 (dd, J = 4.6, 3.1 Hz, 1H), 4.91 (dd, J = 10.9, 5.5 Hz, 1H), 4.17 (dd, J = 10.4, 3.2 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.89 – 3.82 (m, 1H), 3.40 (q, J = 7.0 Hz, 1H), 2.91 (s, 2H), 2.88 (s, 1H), 2.47 (s, 2H).



Parameters		
	Parameter	Value
1	Data File Name	C:\Users\Administrator\Documents\Dissertation\My Spectra\Tosylation Bromine\2\fid
2	Title	
3	Comment	Bruker AV400 Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsu
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	295.1
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	1864
13	Receiver Gain	91600
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1957.9
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

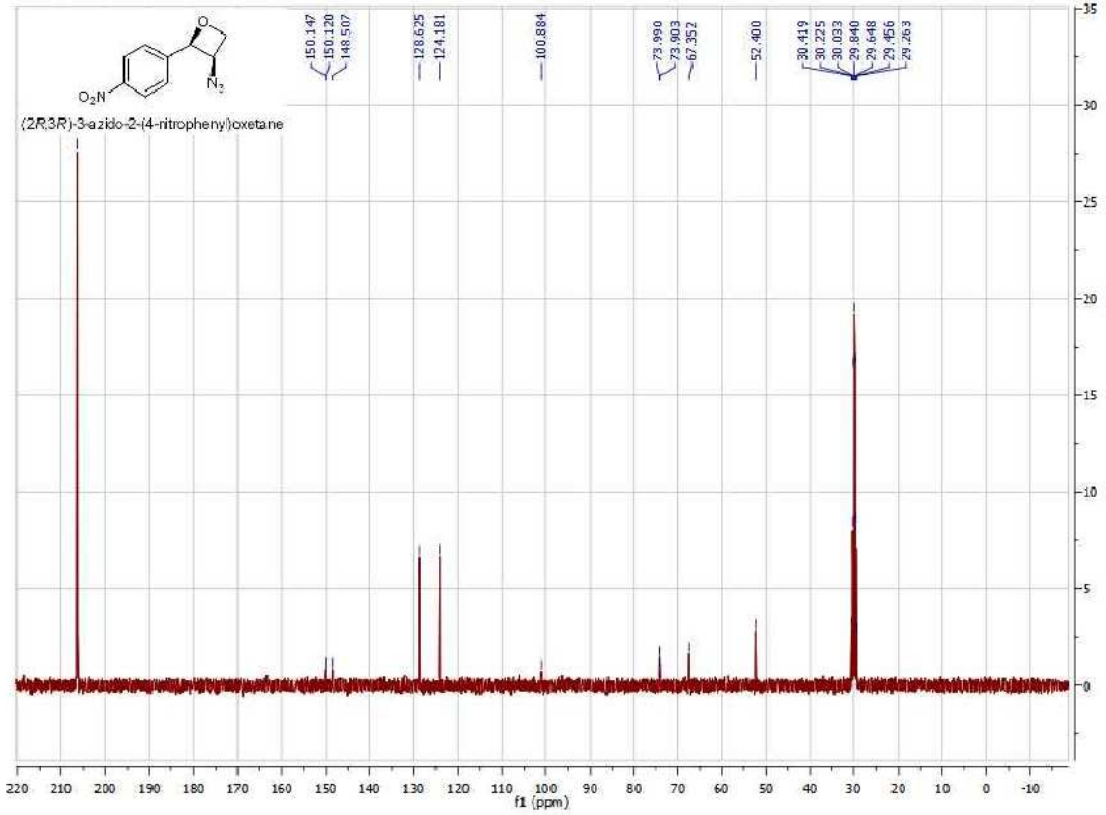
^{13}C NMR (101 MHz, Acetone) δ 205.39, 145.37, 131.30, 130.08, 128.56, 128.32, 128.23, 127.89, 121.24, 72.51, 72.45, 69.33, 65.52, 65.44, 65.23, 29.54, 29.35, 29.16, 28.96, 28.77, 28.58, 28.39, 20.67, 14.72.

Parameters
Parameter
Value
1 Data File Name F:\Data - davide\acylated derivative\RX 2\5d
2 Title
3 Comment Bruker AVANCE Center
4 Origin Bruker BioSpin GmbH
5 Owner nmrsu
6 Spectrometer spect
7 Author
8 Solvent CDCl3
9 Temperature 298.1
10 Pulse Sequence zgpg30
11 Proscansol 16
12 Number of Scans 260
13 Receiver Gain 32800
14 Spectrometer Frequency 100.62
15 Spectral Width 24038.5
16 Lowest Frequency -1946.6
17 Nucleus 13C
18 Acquired Size 32768
19 Spectral Size 65536
13C NMR (101 MHz, CDCl3, δ
145.51, 140.55, 135.07, 132.35,
130.12, 128.09, 127.91, 119.47,
77.43, 77.16, 76.34, 72.83, 68.64,
65.74, 21.79, 14.25, 0.10.
f1 (ppm)



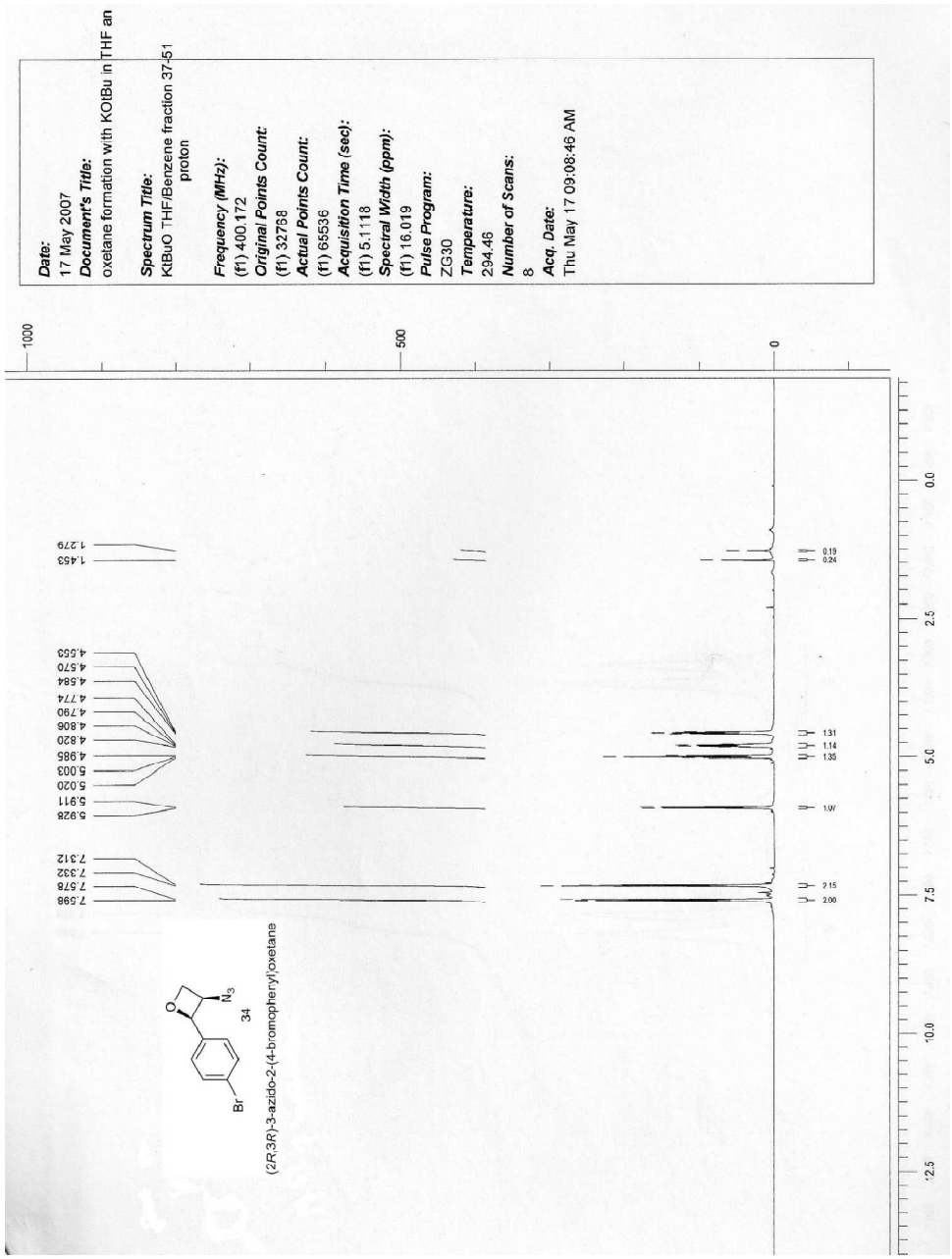
Parameters		
	Parameter	Value
1	Data File Name	G:\ Nitro Oxetane Formation with Cs2CO3 rt\ 1\ fid
2	Title	Bruker AV400 Proton
3	Origin	Bruker BioSpin GmbH
4	Owner	vmbrugn
5	Solvent	Acetone
6	Pulse Sequence	zg30
7	Acquisition Date	2009-05-07T14:42:10
8	Modification Date	
9	Temperature	298.2
10	Number of Scans	8
11	Spectrometer Frequency	400.15
12	Spectral Width	8223.7
13	Lowest Frequency	-1640.8
14	Nucleus	1H
15	Acquired Size	32768
16	Spectral Size	65536

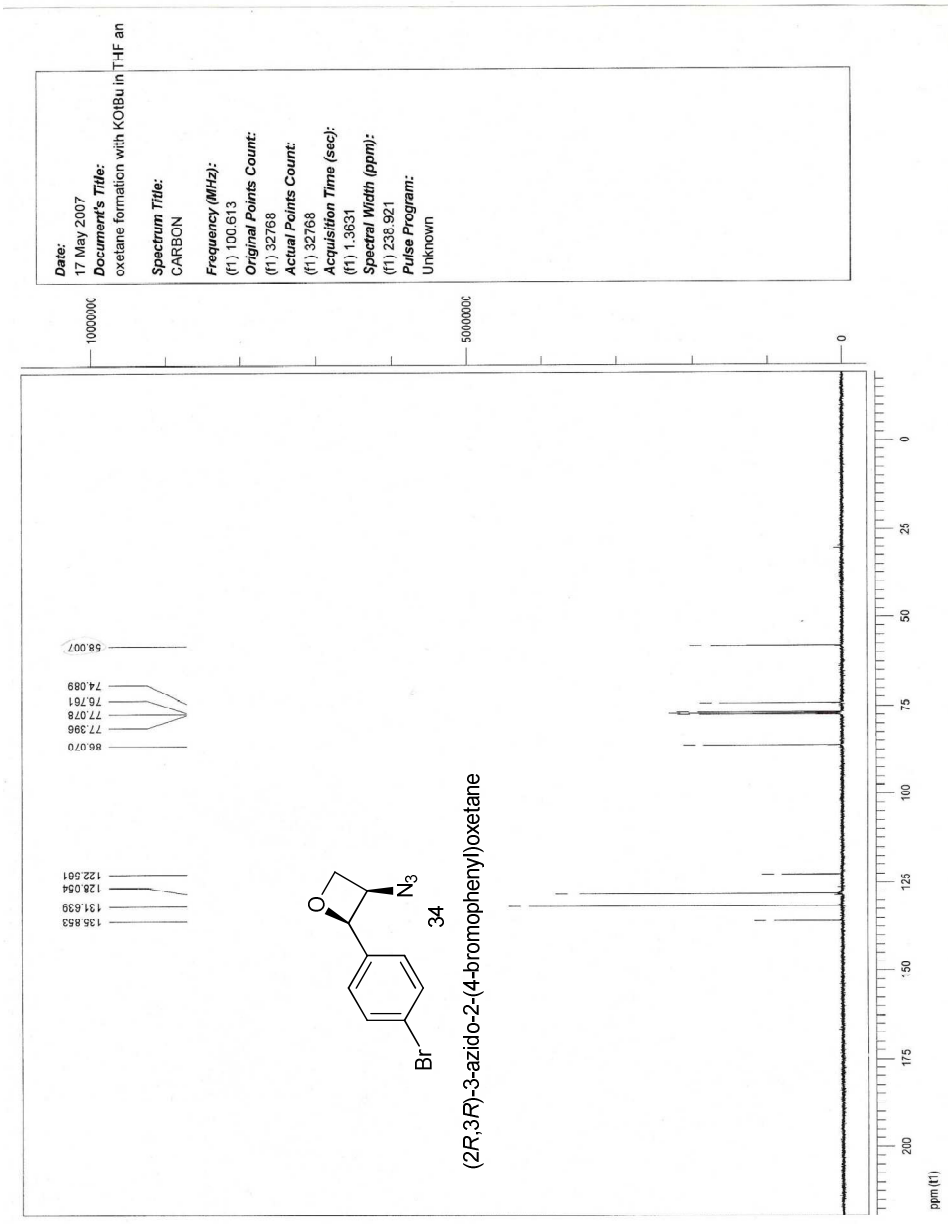
^{1}H NMR (400 MHz, Acetone) δ 8.25 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 5.49 (d, J = 4.7 Hz, 1H), 5.46 (s, 1H), 5.13 (t, J = 4.6 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.83 – 3.80 (m, 1H), 3.63 (dd, J = 13.0, 4.1 Hz, 1H), 3.58 (s, 1H), 3.46 (dd, J = 13.0, 7.9 Hz, 1H), 3.42 – 3.36 (m, 1H), 2.95 (d, J = 12.7 Hz, 2H).

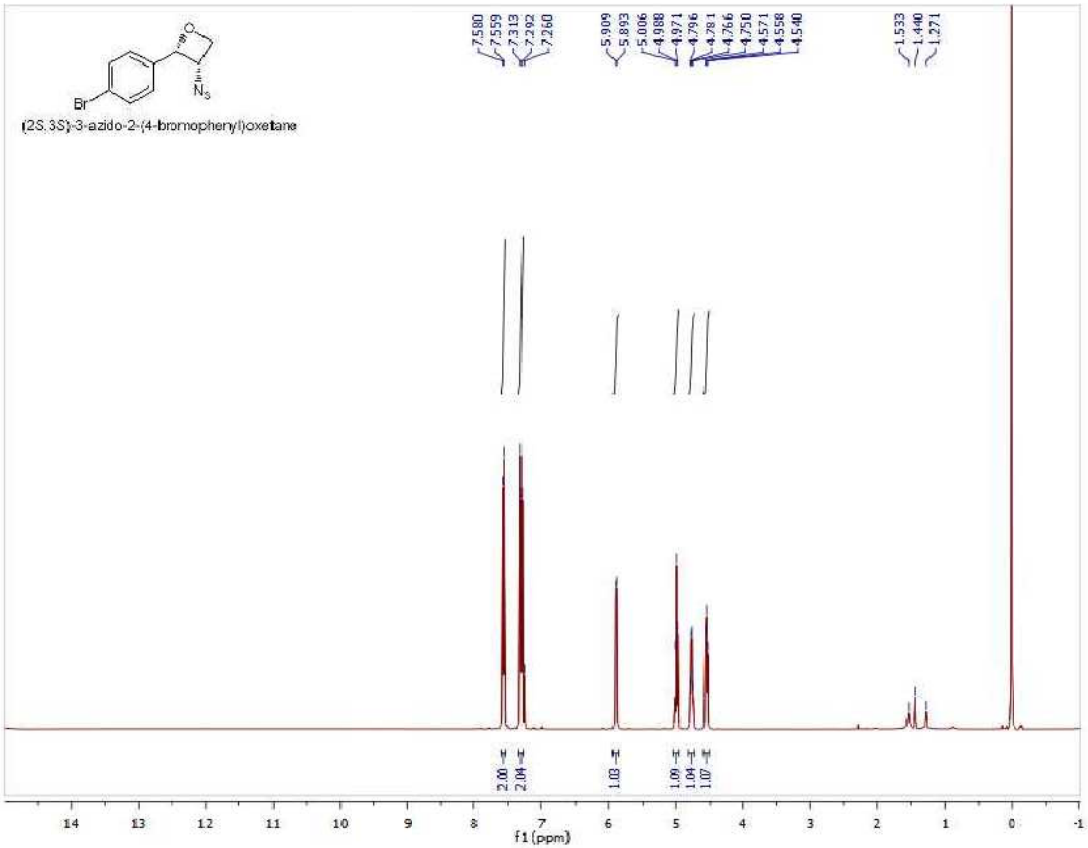


Parameter:		
	Parameter	Value
1	Data File Name	G:\Nitro Oxetane Formation with Ca2CO3 rt\2\fid
2	Title	Bruker AV400 Carbon
3	Origin	Bruker BioSpin GmbH
4	Owner	vmlbraga
5	Solvent	Acetone
6	Pulse Sequence	zgpg30
7	Acquisition Date	2009-05-07T14:54:27
8	Modification Date	
9	Temperature	298.2
10	Number of Scans	150
11	Spectrometer Frequency	100.61
12	Spectral Width	24038.5
13	Lowest Frequency	-1868.3
14	Nucleus	13C
15	Acquired Size	32768
16	Spectral Size	65536

^{13}C NMR (101 MHz, Acetone) δ 150.15, 150.12, 148.51, 128.62, 124.18, 100.88, 73.99, 73.90, 67.35, 52.40.

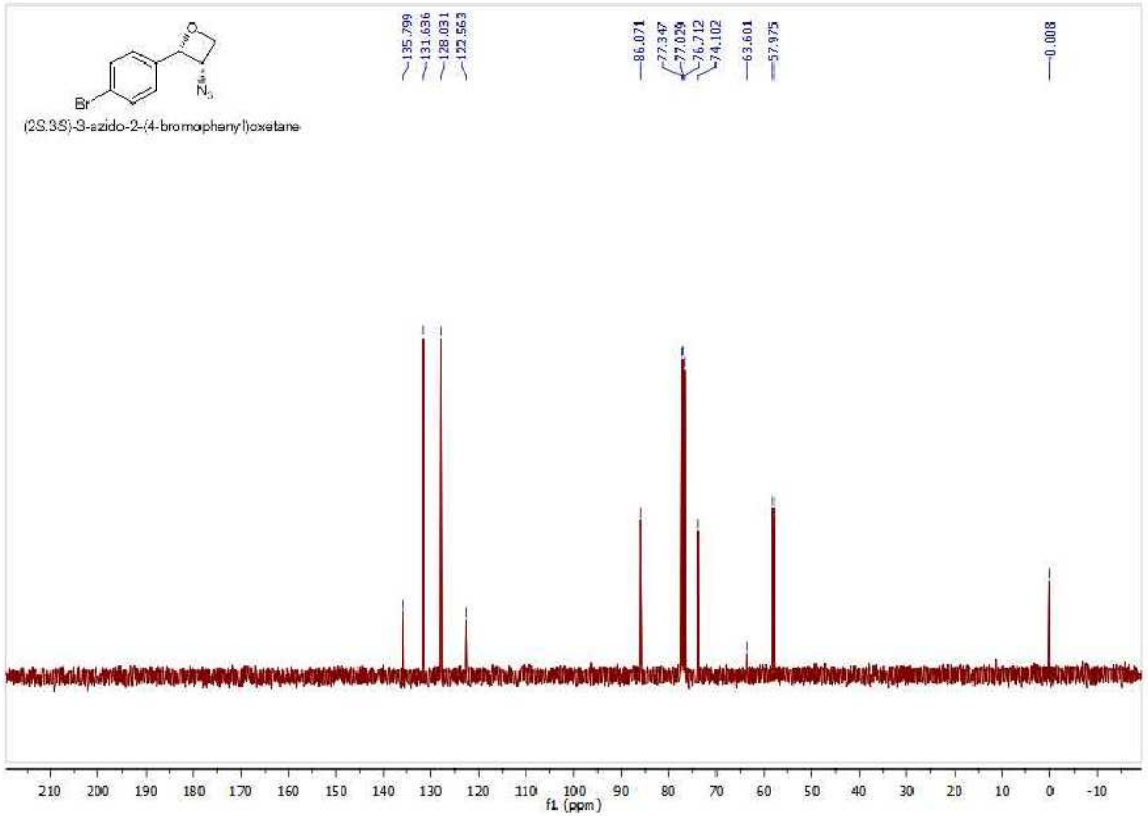

Date:
17 May 2007
Document's Title:
oxetane formation with KOtBu in THF an
Spectrum Title:
KtBuO THF/Benzene fraction 37-51
proton
Frequency (MHz):
(f1) 400.172
Original Points Count:
(f1) 32768
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 5.1118
Spectral Width (ppm):
(f1) 16.019
Pulse Program:
ZG30
Temperature:
294.46
Number of Scans:
8
Acq. Date:
Thu May 17 09:08:46 AM
(2R,3R)-3-azido-2-(4-bromopheryl)oxetane
34
1000
500
0
12.5
10.0
7.5
5.0
2.5
0.0


Date:
17 May 2007
Document's Title:
oxetane formation with KOtBu in THF an
Spectrum Title:
CARBON
Frequency (MHz):
(f1) 100.613
Original Points Count:
(f1) 32768
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 1.3631
Spectral Width (ppm):
(f1) 238.921
Pulse Program:
Unknown
58.007
74.089
76.761
77.078
77.396
86.070
122.561
128.054
131.639
135.853
O
N3
Br
34
(2R,3R)-3-azido-2-(4-bromophenyl)oxetane
ppm (t1)



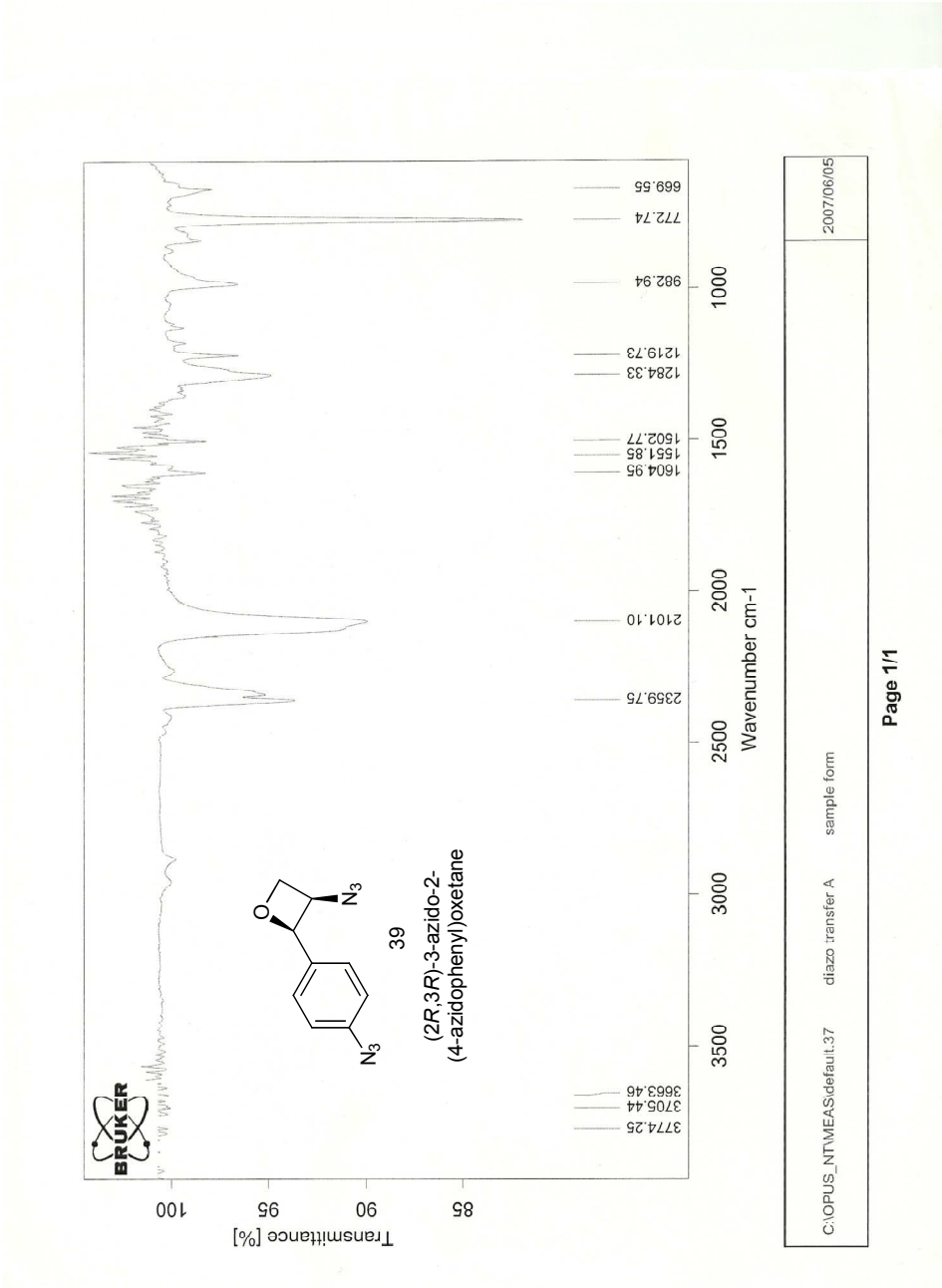
Parameters		
	Parameter	Value
1	Data File Name	F:\ Data \bromoaine oxetane SS 2\ 1\ fid
2	Title	AF-07-041_Run A
3	Origin	Bruker BioSpin GmbH
4	Owner	Rob Smith
5	Solvent	CDCl3
6	Pulse Sequence	zg30
7	Acquisition Date	2010-01-21T14:05:09
8	Temperature	311.4
9	Number of Scans	13
10	Spectrometer Frequency	400.17
11	Nucleus	1H

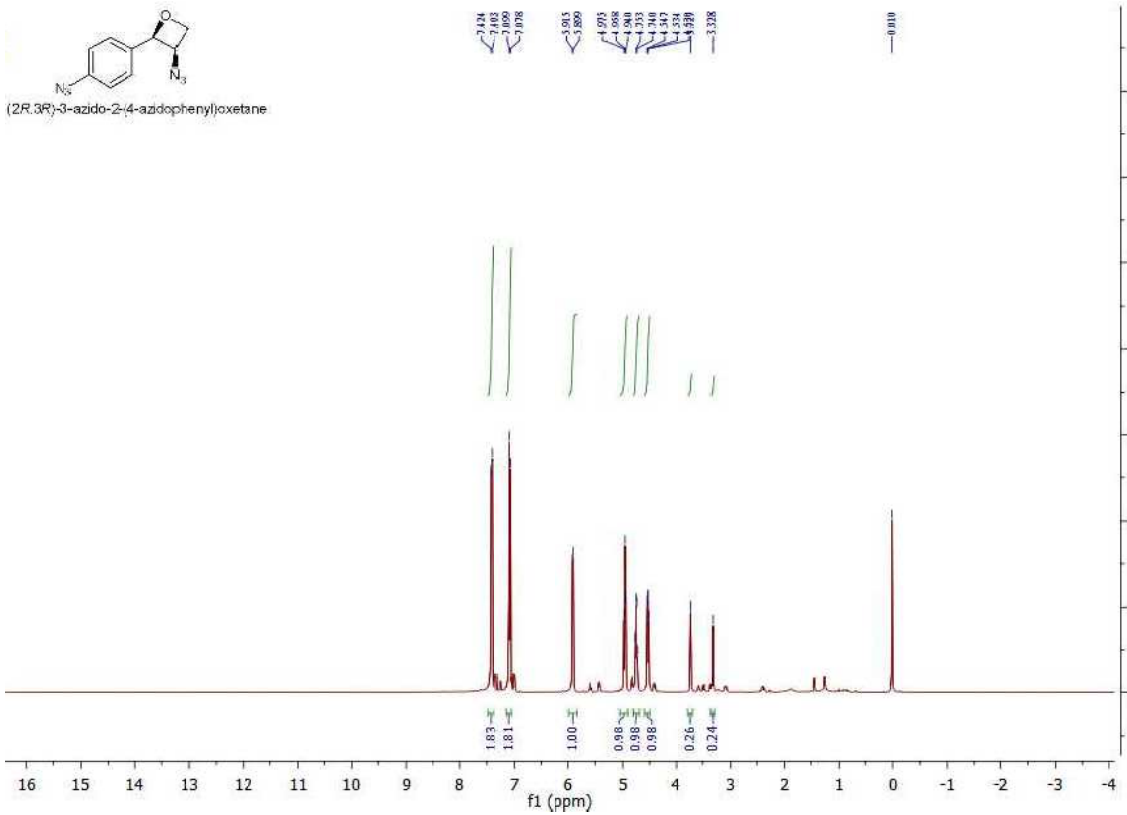
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 5.90 (d, J = 6.6 Hz, 1H), 4.99 (t, J = 7.0 Hz, 1H), 4.77 (dd, J = 12.1, 6.2 Hz, 1H), 4.60 – 4.52 (m, 1H).



Parameters		
	Parameter	Value
1	Data File Name	F:\Data\bromine oxetane 8S\2\fid
2	Title	AF-07-041_Rx n.A
3	Origin	Bruker BioSpin GmbH
4	Owner	Rob Smith
5	Solvent	CDCl3
6	Pulse Sequence	zgpg30
7	Acquisition Date	2010-01-22T11:01:08
8	Temperature	298.2
9	Number of Scans	512
10	Spectrometer Frequency	100.62
11	Nucleus	13C

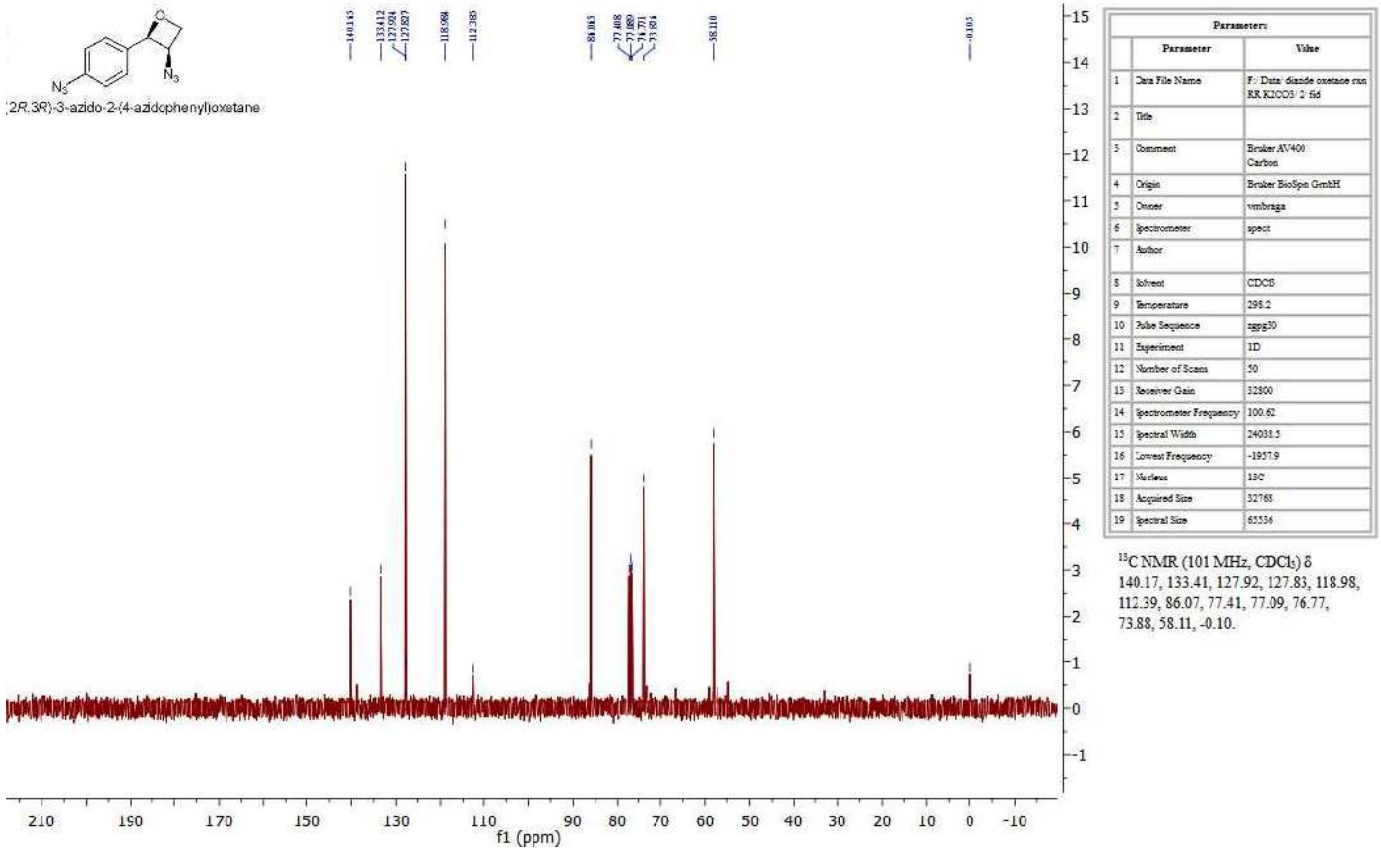
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.80, 131.64, 128.03, 122.56, 86.07, 77.35, 77.03, 76.71, 74.10, 63.60, 57.97, -0.01.


BRUKER
Transmittance [%]
100
95
90
85
3500
3000
2500
2000
1500
1000
Wavenumber cm-1
3774.25
3705.44
3663.46
2359.75
2101.10
1604.95
1551.85
1502.77
1284.33
1219.73
982.94
772.74
669.55
39
(2R,3R)-3-azido-2-
(4-azidophenyl)oxetane
C:\OPUS_NT\MEAS\default.37
diazo transfer A
sample form
2007/06/05
Page 1/1



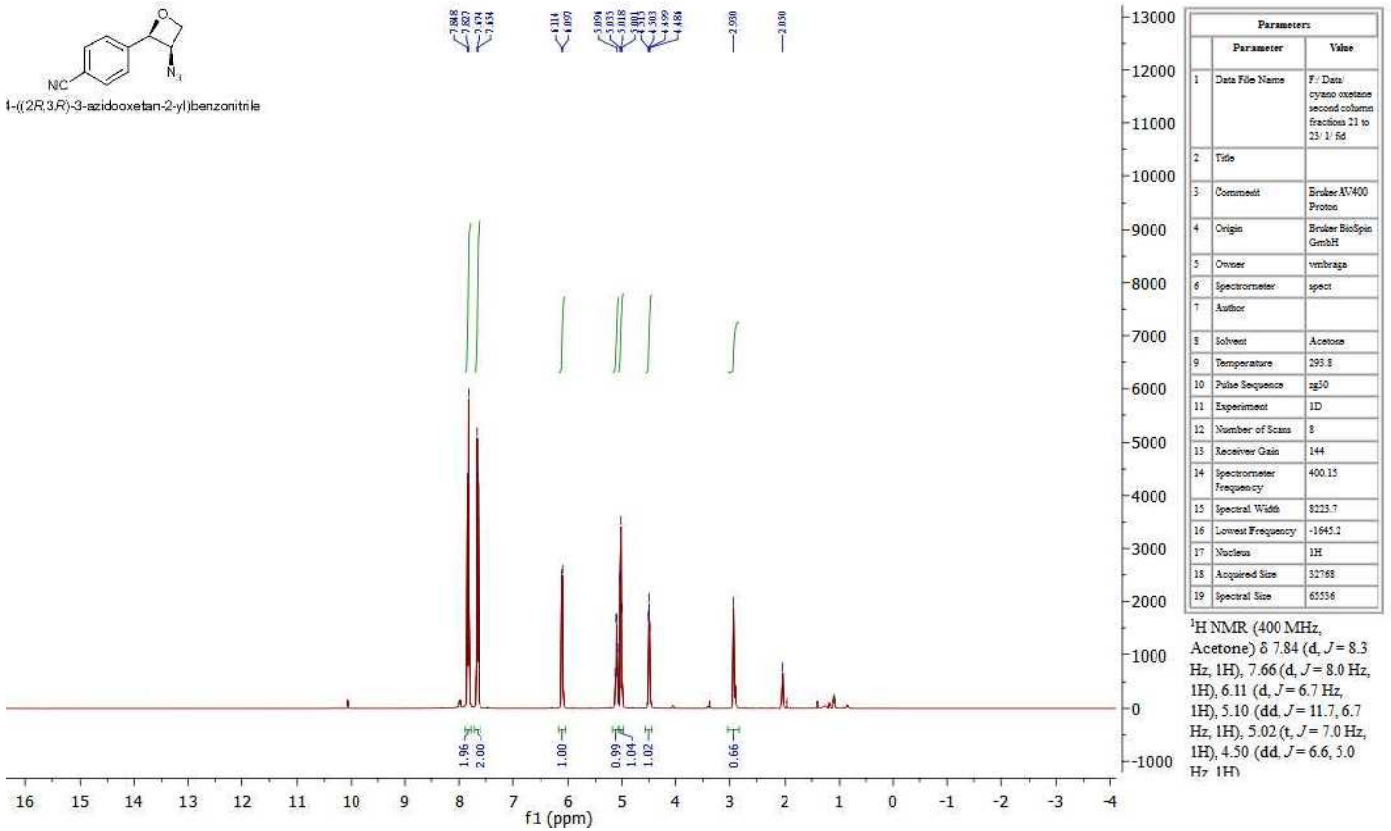
Parameters		
	Parameter	Value
1	Data File Name	F:/ Data/ diazide oxetane rxn RR K2CO3/ 1/ fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	CDCl3
9	Temperature	298.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	8
13	Receiver Gain	72
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1645.2
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 5.91 (d, J = 6.6 Hz, 1H), 4.96 (t, J = 7.0 Hz, 1H), 4.75 (dd, J = 11.9, 6.5 Hz, 1H), 4.53 (dd, J = 7.1, 5.2 Hz, 1H).



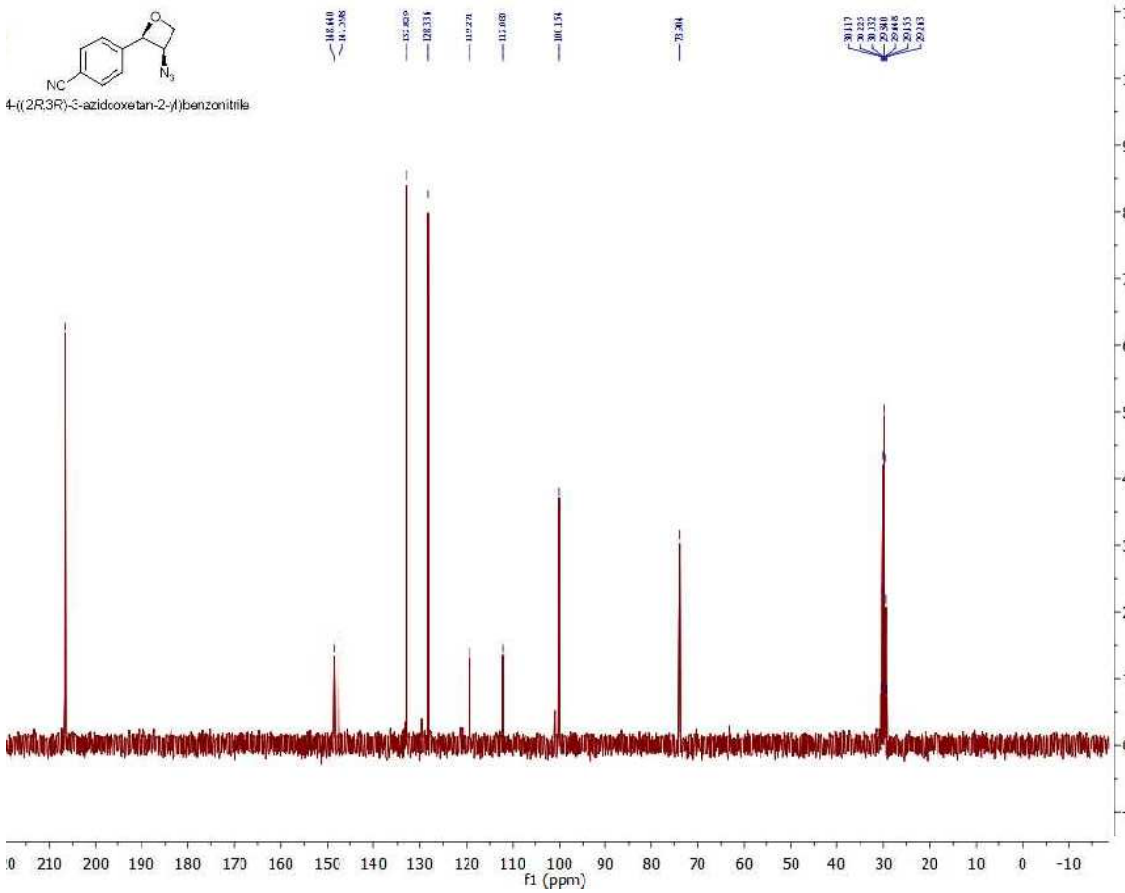
Parameters		
	Parameter	Value
1	Data File Name	F:\ Data\ diazide oxetane exo RR K2CO3\ 2\ fid
2	Title	
3	Comment	Bruker AV400 Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	CDCl3
9	Temperature	298.2
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	50
13	Receiver Gain	32800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1957.9
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.17, 133.41, 127.92, 127.83, 118.98, 112.39, 86.07, 77.41, 77.09, 76.77, 73.88, 58.11, -0.10.



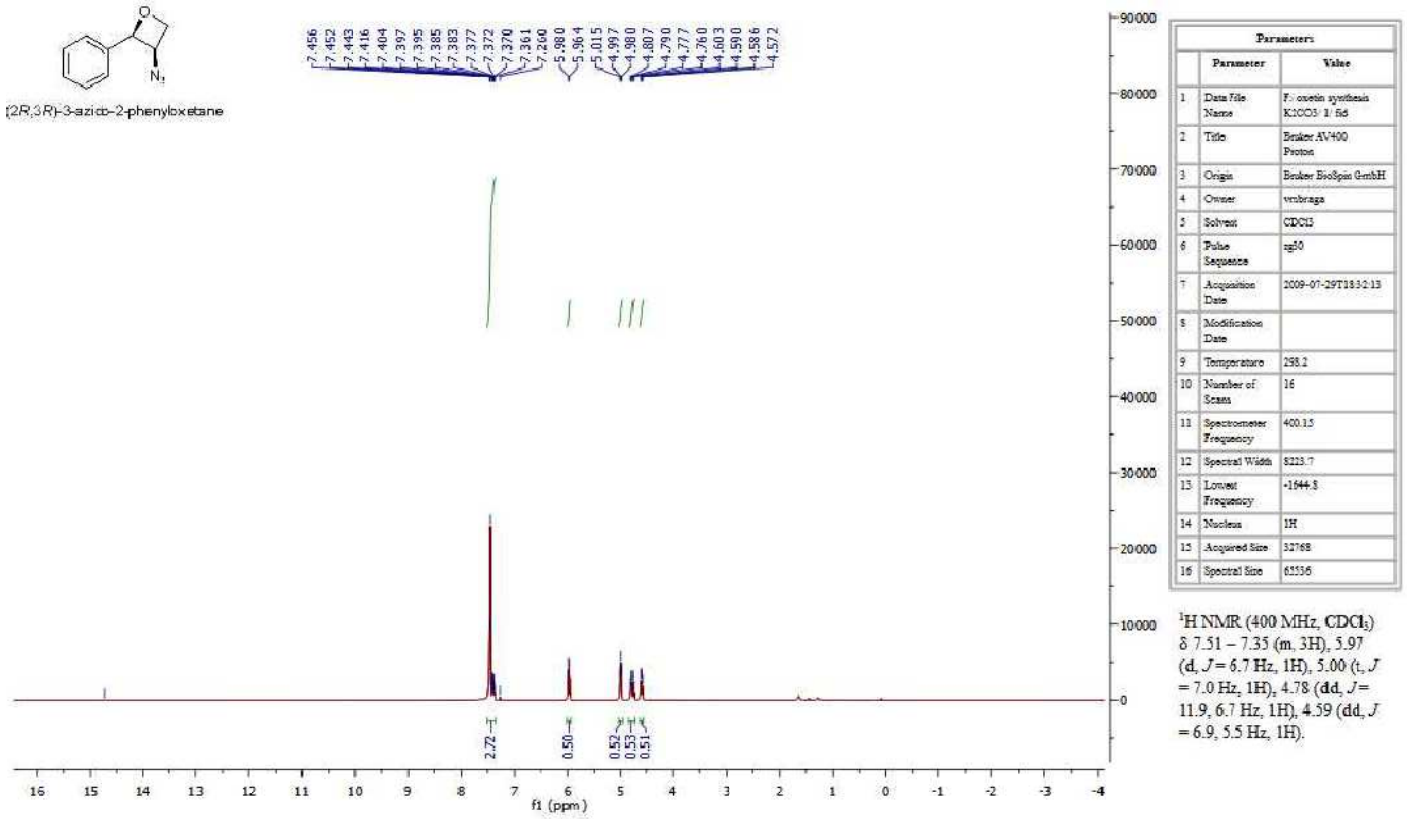
Parameters		
	Parameter	Value
1	Data File Name	F:/ Data/ cyano oxetane second column fractions 21 to 23/ 1/ 5d
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	293.8
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	8
13	Receiver Gain	144
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1645.2
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

^{1}H NMR (400 MHz, Acetone) δ 7.84 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 6.11 (d, J = 6.7 Hz, 1H), 5.10 (dd, J = 11.7, 6.7 Hz, 1H), 5.02 (t, J = 7.0 Hz, 1H), 4.50 (dd, J = 6.6, 5.0 Hz, 1H)



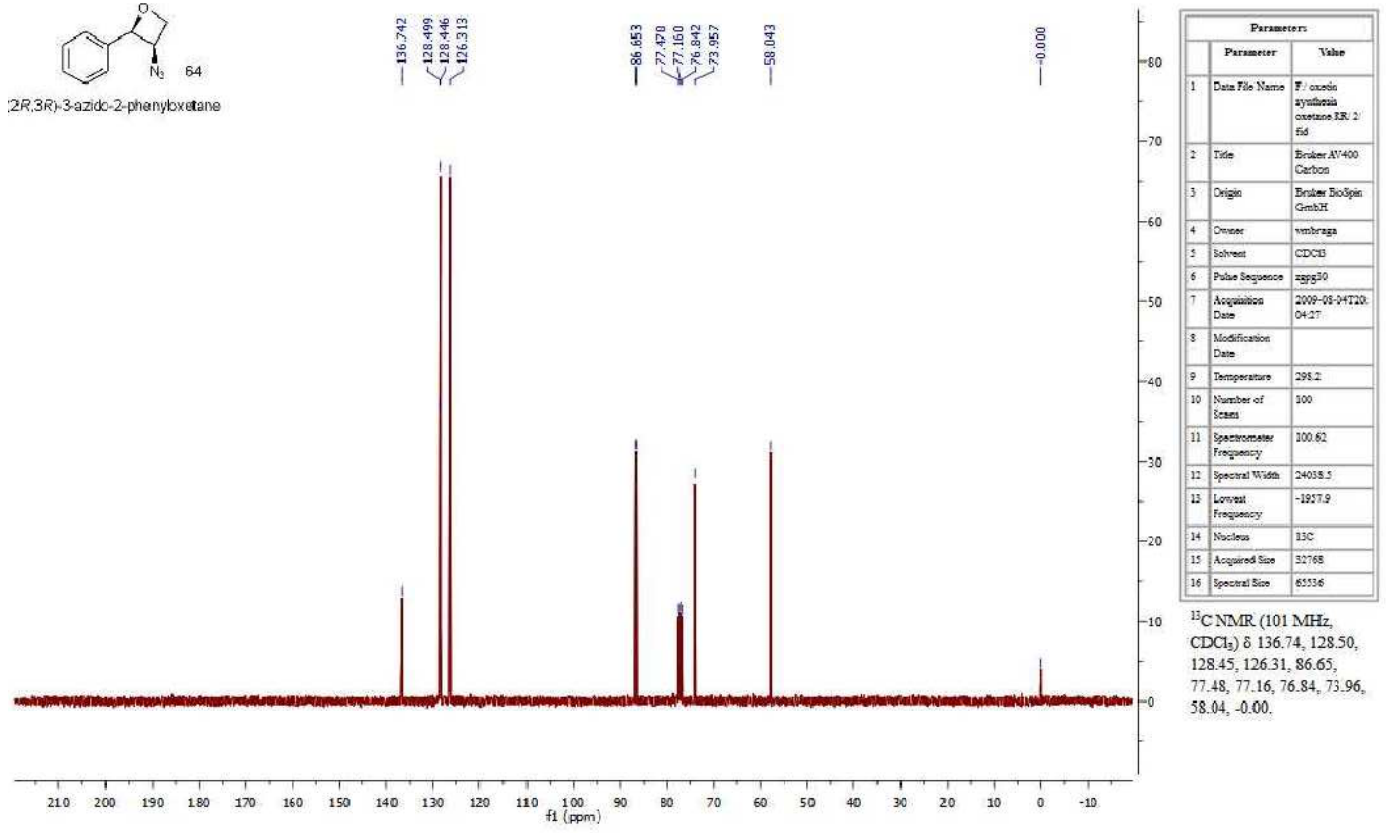
Parameters		
	Parameter	Value
1	Data File Name	F:\ Data\ cyano oxetane fraction 1 to 3 carbon\ 2\ fid
2	Title	
3	Comment	BrukerAV400 Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	294.1
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	34
13	Receiver Gain	32800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1851.4
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

^{13}C NMR (101 MHz Acetone) δ 206.60, 148.64, 147.60, 132.83, 128.34, 119.27, 112.08, 100.15, 73.90, 30.42, 30.22, 30.03, 29.84, 29.65, 29.46, 29.26.



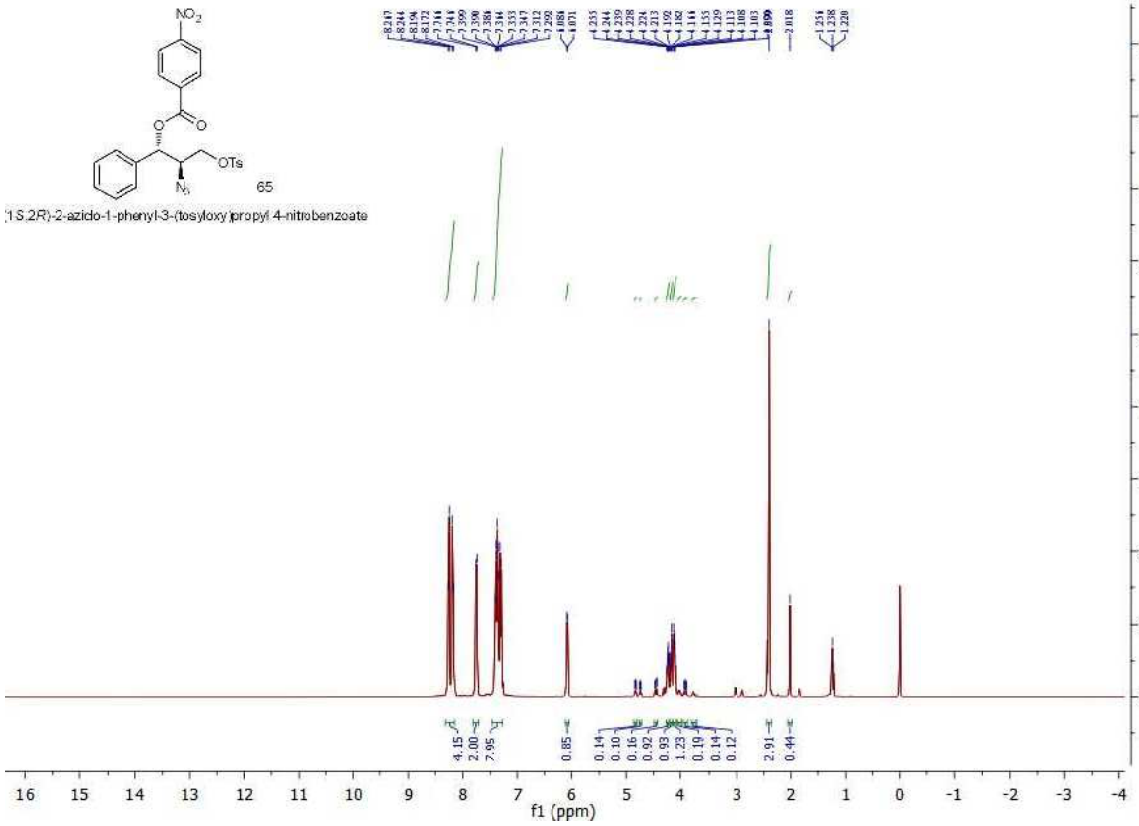
Parameters		
	Parameter	Value
1	Data File Name	F:\ oxetin synthesis K2CO3\ 1\ fid
2	Title	Bruker AV400 Proton
3	Origin	Bruker BioSpin GmbH
4	Owner	vrubraga
5	Solvent	CDCl3
6	Pulse Sequence	zg30
7	Acquisition Date	2009-07-29T18:32:13
8	Modification Date	
9	Temperature	298.2
10	Number of Scans	16
11	Spectrometer Frequency	400.15
12	Spectral Width	8223.7
13	Lowest Frequency	-1644.8
14	Nucleus	1H
15	Acquired Size	32768
16	Spectral Size	65536

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.35 (m, 3H), 5.97 (**d**, *J* = 6.7 Hz, 1H), 5.00 (t, *J* = 7.0 Hz, 1H), 4.78 (**dd**, *J* = 11.9, 6.7 Hz, 1H), 4.59 (**dd**, *J* = 6.9, 5.5 Hz, 1H).



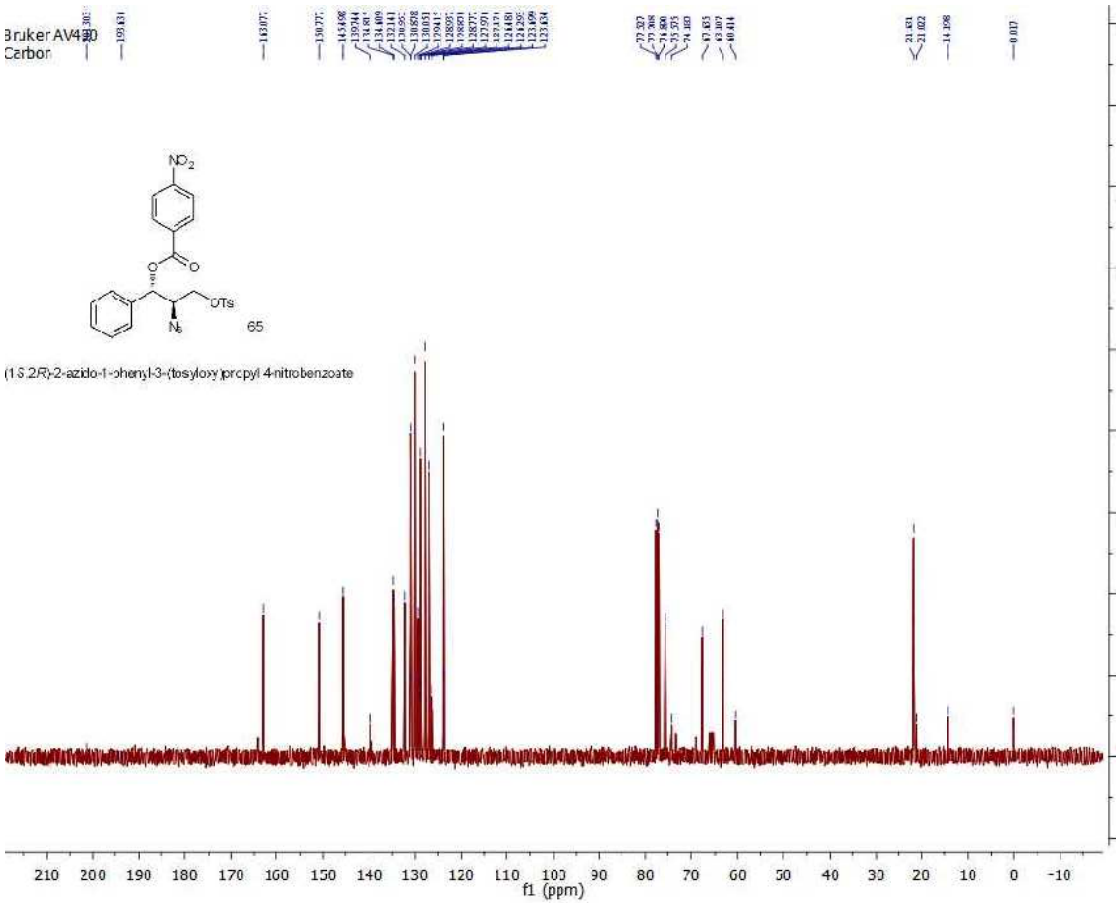
Parameters		
	Parameter	Value
1	Data File Name	F:/ oxesin synthesis oxetane ER/ 2/ fid
2	Title	Bruker AV400 Carbon
3	Origin	Bruker BioSpin GmbH
4	Owner	vembraga
5	Solvent	CDCl3
6	Pulse Sequence	zgpg30
7	Acquisition Date	2009-08-04T20:04:27
8	Modification Date	
9	Temperature	298.2
10	Number of Scans	100
11	Spectrometer Frequency	100.62
12	Spectral Width	24038.5
13	Lowest Frequency	-1957.9
14	Nucleus	13C
15	Acquired Size	32768
16	Spectral Size	65536

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.74, 128.50, 128.45, 126.31, 86.65, 77.48, 77.16, 76.84, 73.96, 58.04, -0.00.



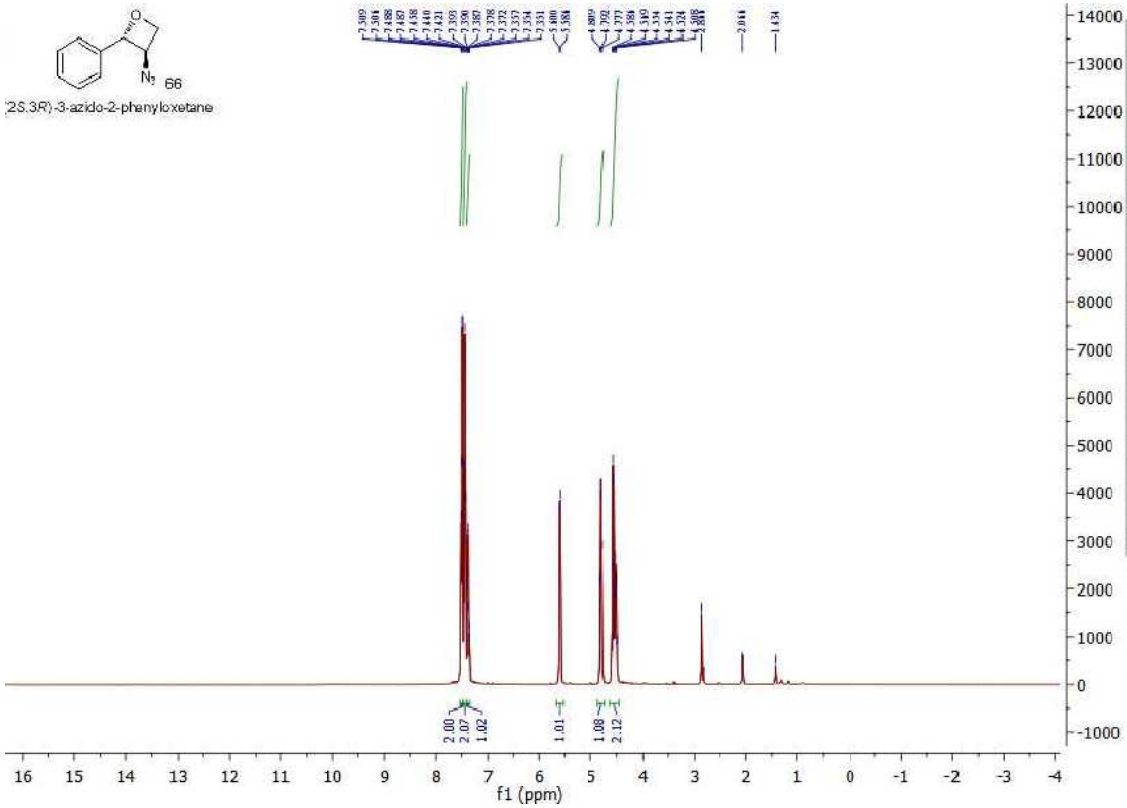
Parameters		
	Parameter	Value
1	Data File Name	F:\ Data\ Nmrs book9 pg97 fraction33\ 1\ fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vembaga
6	Spectrometer	spect
7	Author	
8	Solvent	CDCl3
9	Temperature	298.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	8
13	Receiver Gain	72
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1640.8
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (**dd**, J = 28.9, 8.9 Hz, 4H), 7.76 (**d**, J = 8.3 Hz, 2H), 7.36 (**ddd**, J = 24.5, 13.7, 5.8 Hz, 8H), 6.08 (**d**, J = 6.0 Hz, 1H), 4.23 (**td**, J = 6.3, 4.4 Hz, 1H), 4.17 (**dd**, J = 10.5, 4.3 Hz, 1H), 4.15 – 4.08 (m, 1H), 2.40 (s, 3H).



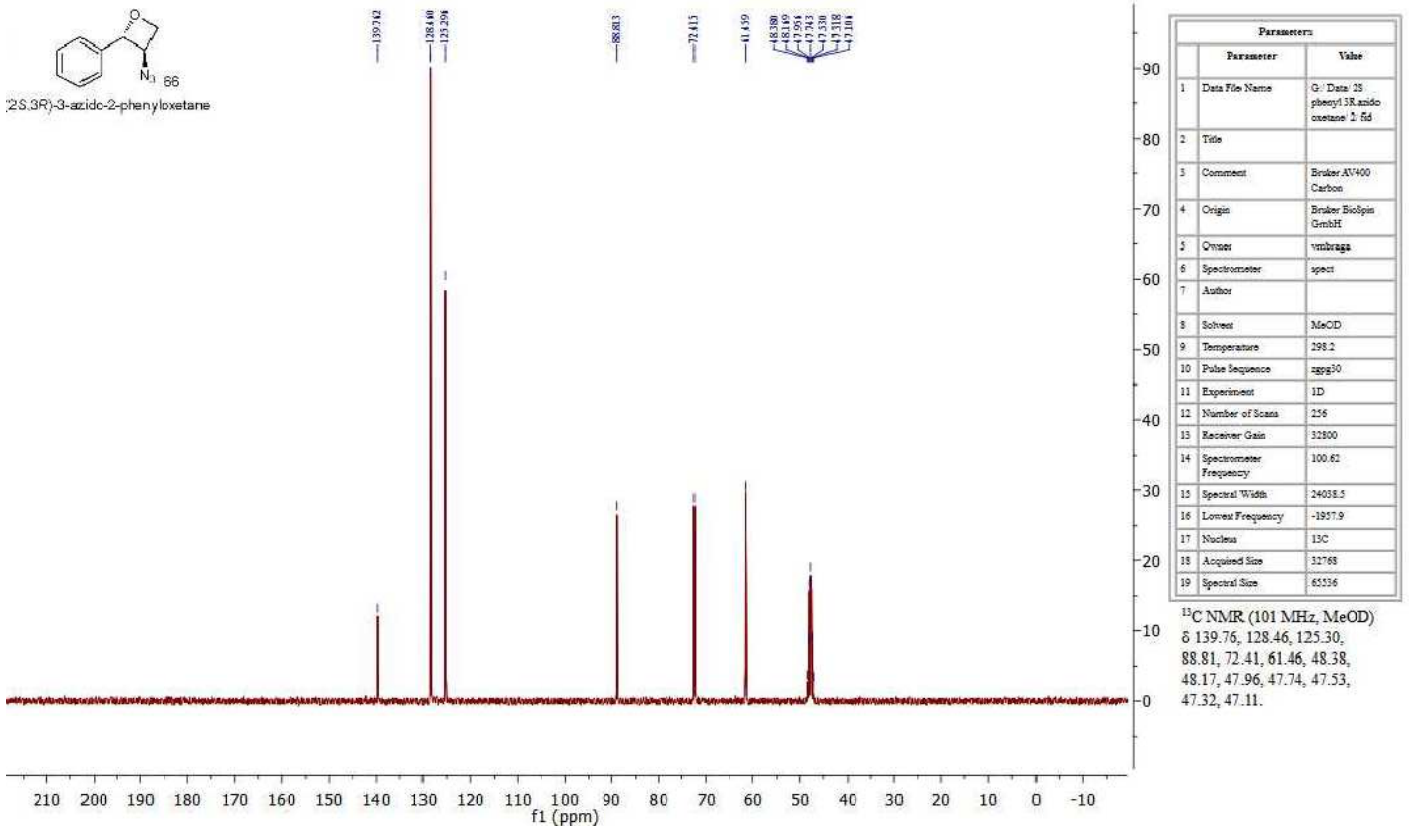
Parameters		
	Parameter	Value
1	Data File Name	F:\Data\Mitra book9\pg97\fraction35\2\fid
2	Title	
3	Comment	Bruker AV400 Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsupa
6	Spectrometer	spect
7	Author	
8	Solvent	CDCl3
9	Temperature	298.2
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	256
13	Receiver Gain	32800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1957.9
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.30, 193.64, 163.08, 150.78, 145.50, 139.74, 134.82, 134.61, 132.14, 130.95, 130.88, 130.05, 129.41, 128.94, 128.87, 128.78, 127.98, 127.18, 126.49, 126.29, 123.70, 123.63, 77.53, 77.21, 76.89, 75.57, 74.18, 67.63, 63.11, 60.41, 21.63, 21.02, 14.28, 0.02.



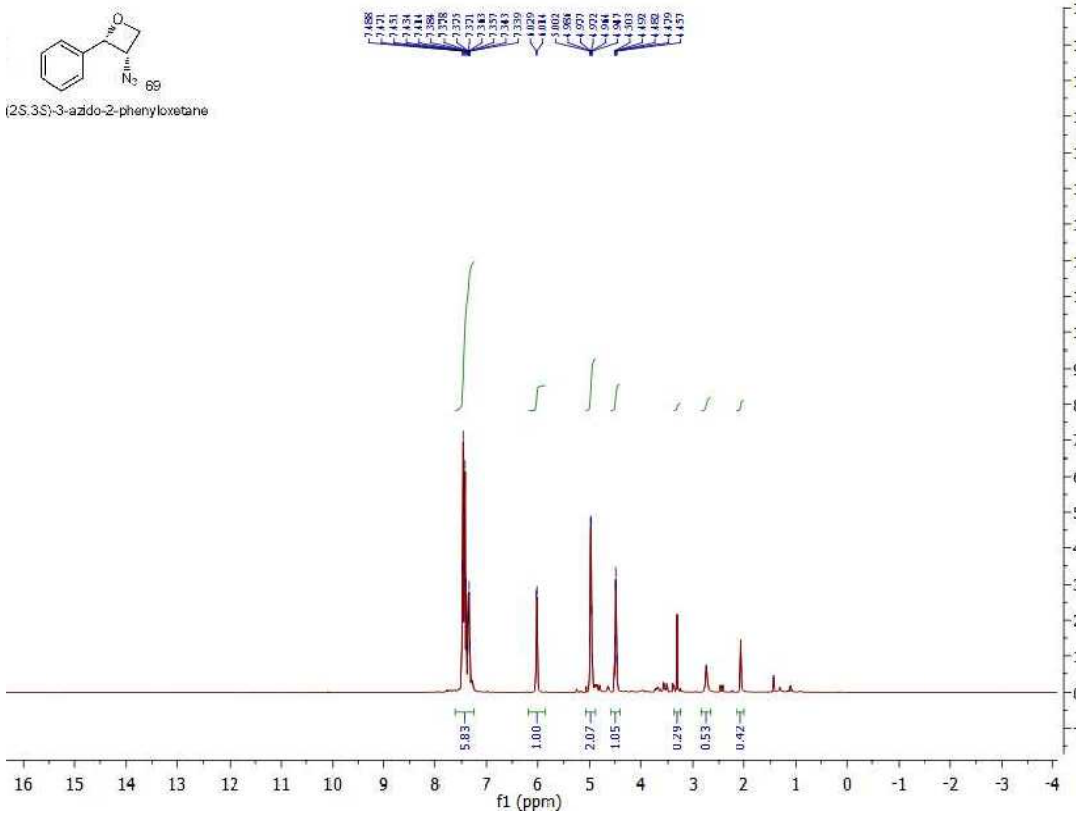
Parameters		
	Parameter	Value
1	Data File Name	G:/ Data/ oxetane 2R,3S/ 1/ fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	apoct
7	Author	
8	Solvent	Acetone
9	Temperature	298.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	16
13	Receiver Gain	72
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1640.8
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

^{1}H NMR (400 MHz, Acetone) δ 7.50 (dd, J = 8.0, 1.1 Hz, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.37 (ddd, J = 8.2, 2.6, 1.3 Hz, 1H), 5.59 (d, J = 5.7 Hz, 1H), 4.79 (t, J = 6.6 Hz, 1H), 4.64 – 4.46 (m, 2H).



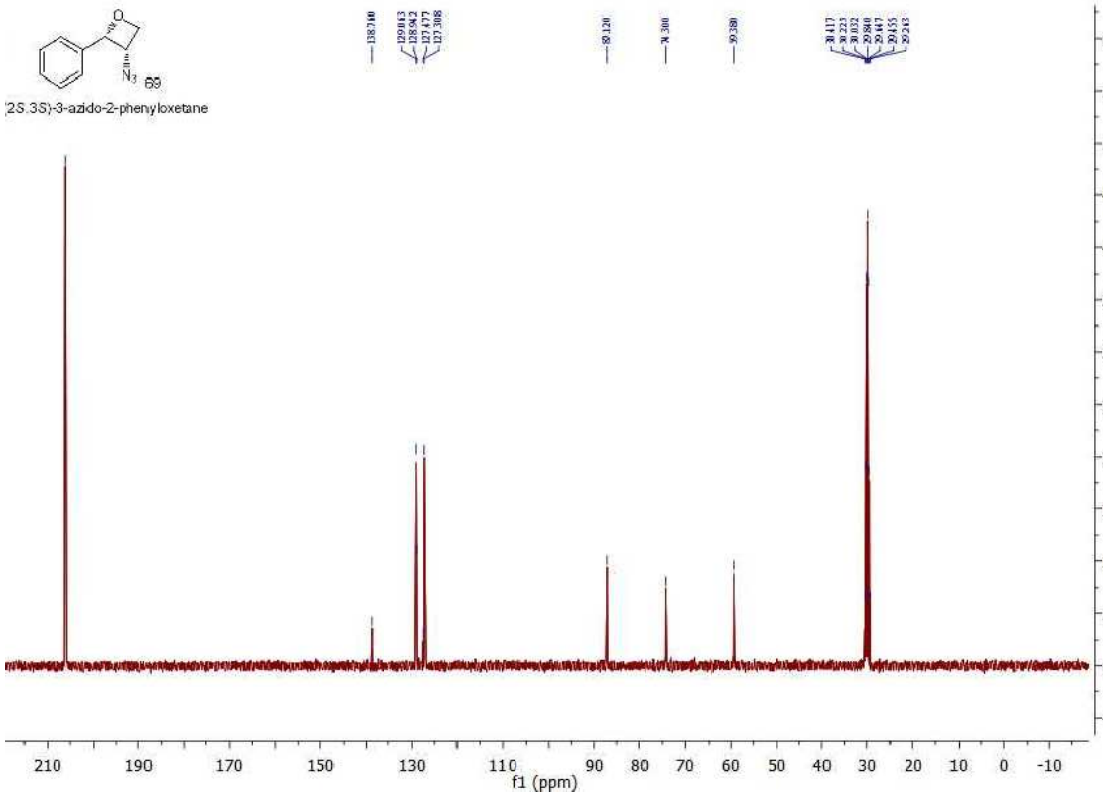
Parameters		
	Parameter	Value
1	Data File Name	G:\Data\2S phenyl 3R azido oxetane\2\fid
2	Title	
3	Comment	Bruker AV400 Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	MeOD
9	Temperature	298.2
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	256
13	Receiver Gain	32800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1957.9
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

^{13}C NMR (101 MHz, MeOD) δ 139.76, 128.46, 125.30, 88.81, 72.41, 61.46, 48.38, 48.17, 47.96, 47.74, 47.53, 47.32, 47.11.



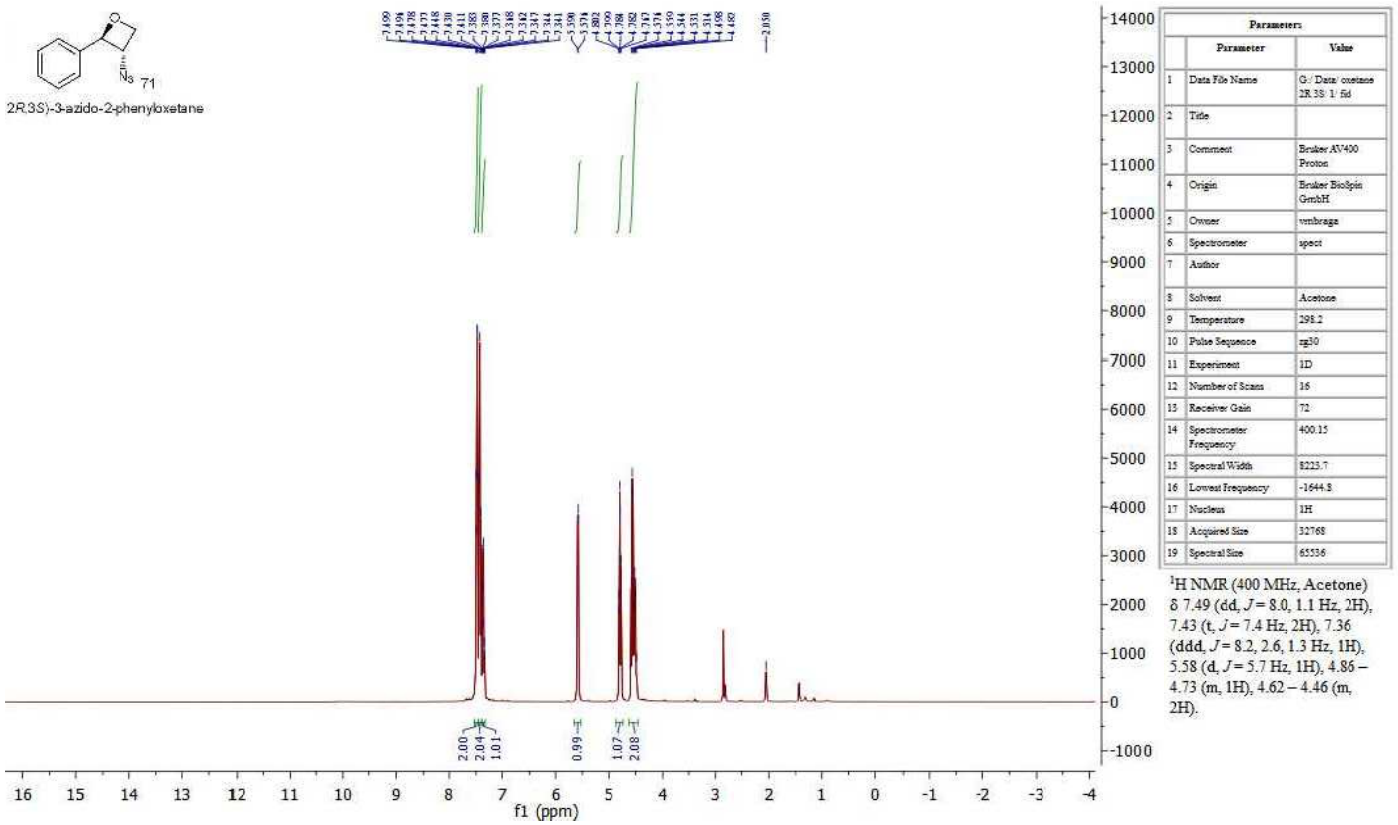
Parameters		
	Parameter	Value
1	Data File Name	G:\Data\2 S phenyl 3 S azido oxetane\1\fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	apect
7	Author	
8	Solvent	Acetone
9	Temperature	313.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	16
13	Receiver Gain	161
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1640.8
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

^{1}H NMR (400 MHz, Acetone) δ 7.62 – 7.26 (m, 6H), 6.02 (d, J = 5.9 Hz, 1H), 5.08 – 4.89 (m, 2H), 4.58 – 4.40 (m, 1H).



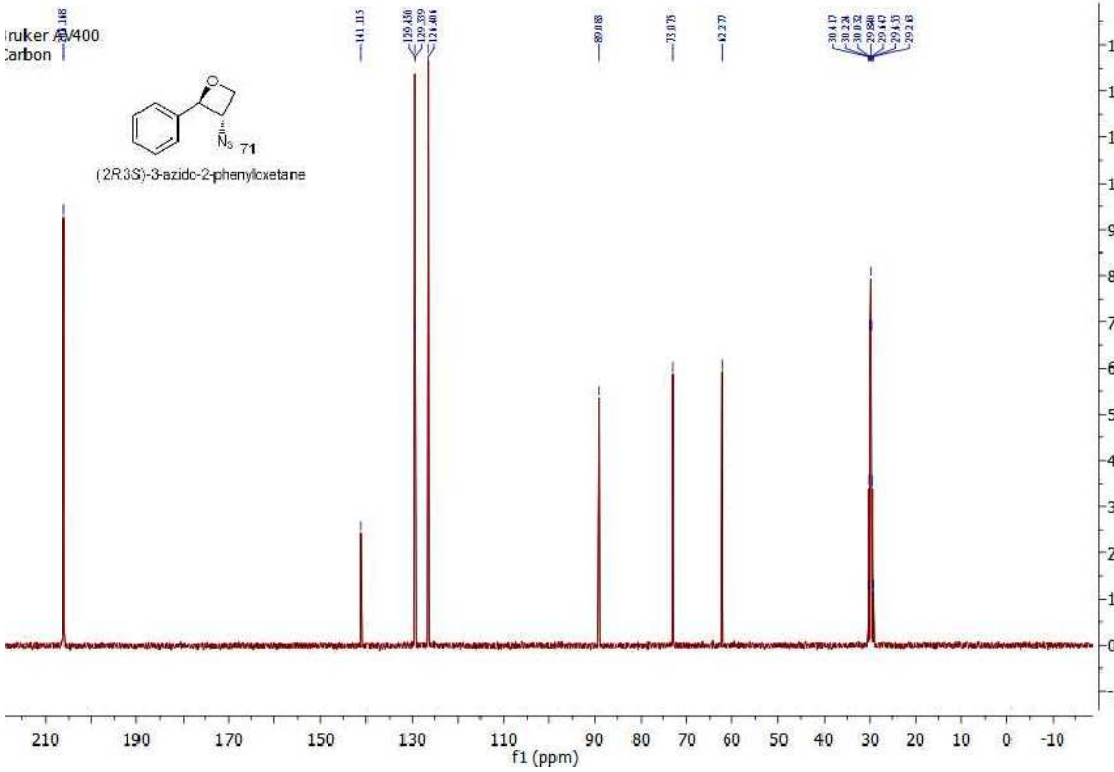
Parameters		
	Parameter	Value
1	Data File Name	G:\Data\2 S phenyl 3 S azido oxetane\2\fid
2	Title	
3	Comment	Bruker AV400 Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	vnbraga
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	313.2
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	256
13	Receiver Gain	32800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1861.7
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

^{13}C NMR (101 MHz, Acetone) δ 206.06, 138.76, 129.06, 128.94, 127.48, 127.31, 87.12, 74.30, 59.38, 30.42, 30.22, 30.03, 29.84, 29.65, 29.45, 29.26.



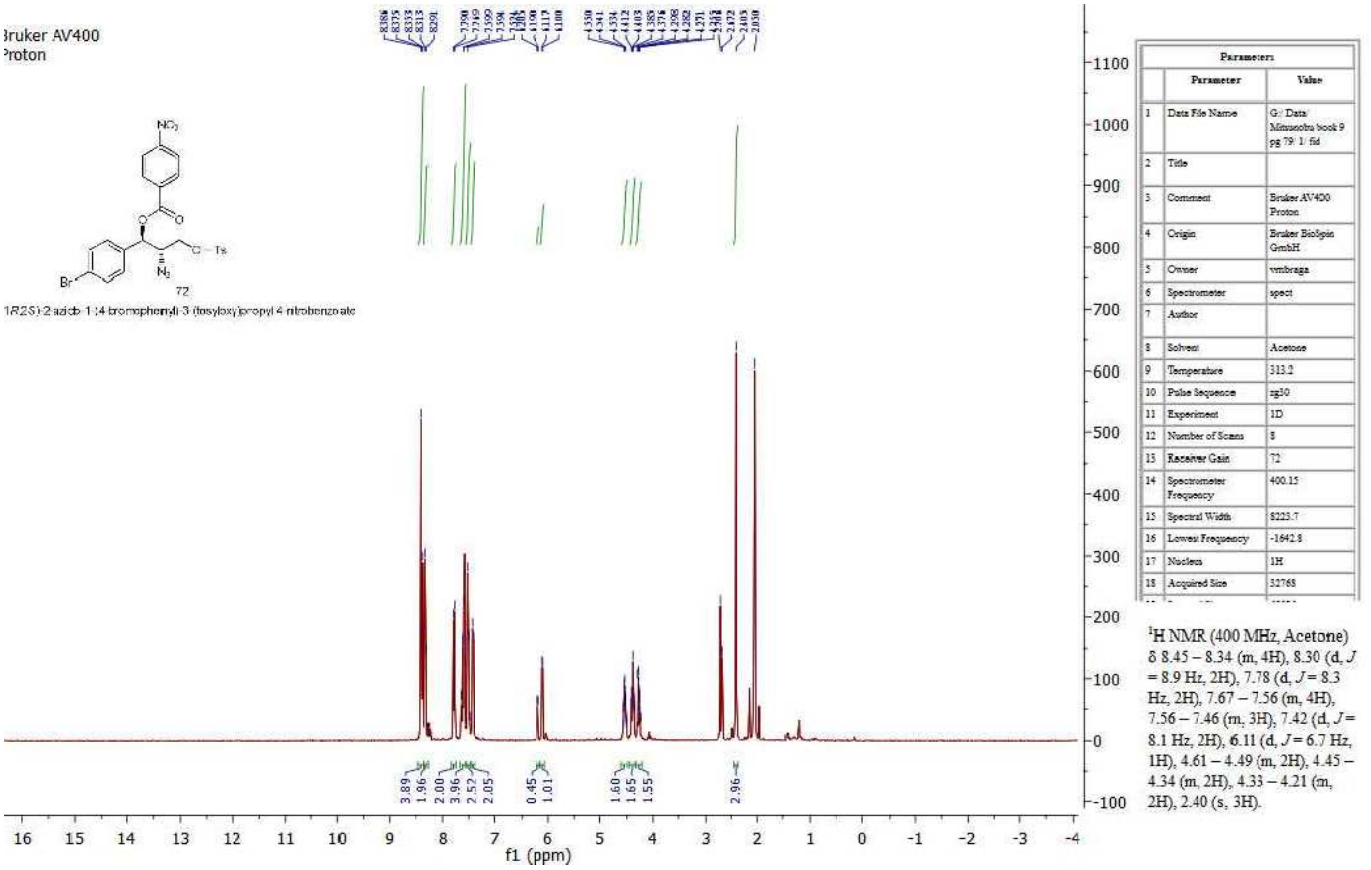
Parameters		
	Parameter	Value
1	Data File Name	G:/Data/ oxetane 2R 3S/ 1/ fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vanbraga
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	298.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	16
13	Receiver Gain	72
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1644.8
17	Nucleus	1H
18	Acquired Size	32768
19	Spectral Size	65536

^{1}H NMR (400 MHz, Acetone) δ 7.49 (dd, J = 8.0, 1.1 Hz, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.36 (ddd, J = 8.2, 2.6, 1.3 Hz, 1H), 5.58 (d, J = 5.7 Hz, 1H), 4.86 – 4.73 (m, 1H), 4.62 – 4.46 (m, 2H).



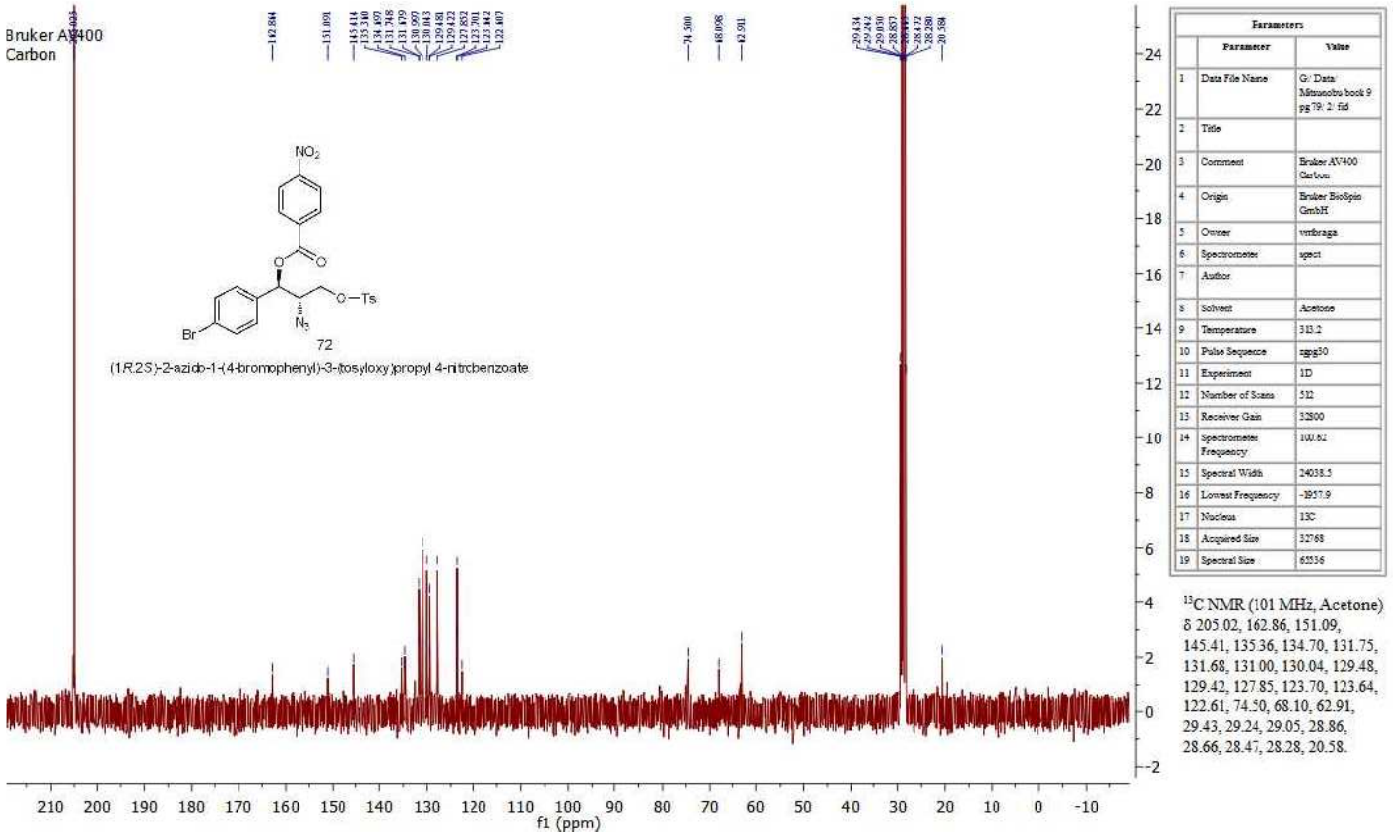
Parameters		
	Parameter	Value
1	Data File Name	G:\Data\oxetane 2R 3S 2\fid
2	Title	
3	Comment	Bruker AV400 Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	vmlbraga
6	Spectrometer	specl
7	Author	
8	Solvent	Acetone
9	Temperature	298.2
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	212
13	Receiver Gain	32800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-1874.1
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

^{13}C NMR (101 MHz, Acetone) δ 206.17, 141.11, 129.45, 129.34, 126.41, 89.08, 73.08, 62.28, 30.42, 30.22, 30.03, 29.84, 29.65, 29.45, 29.26.



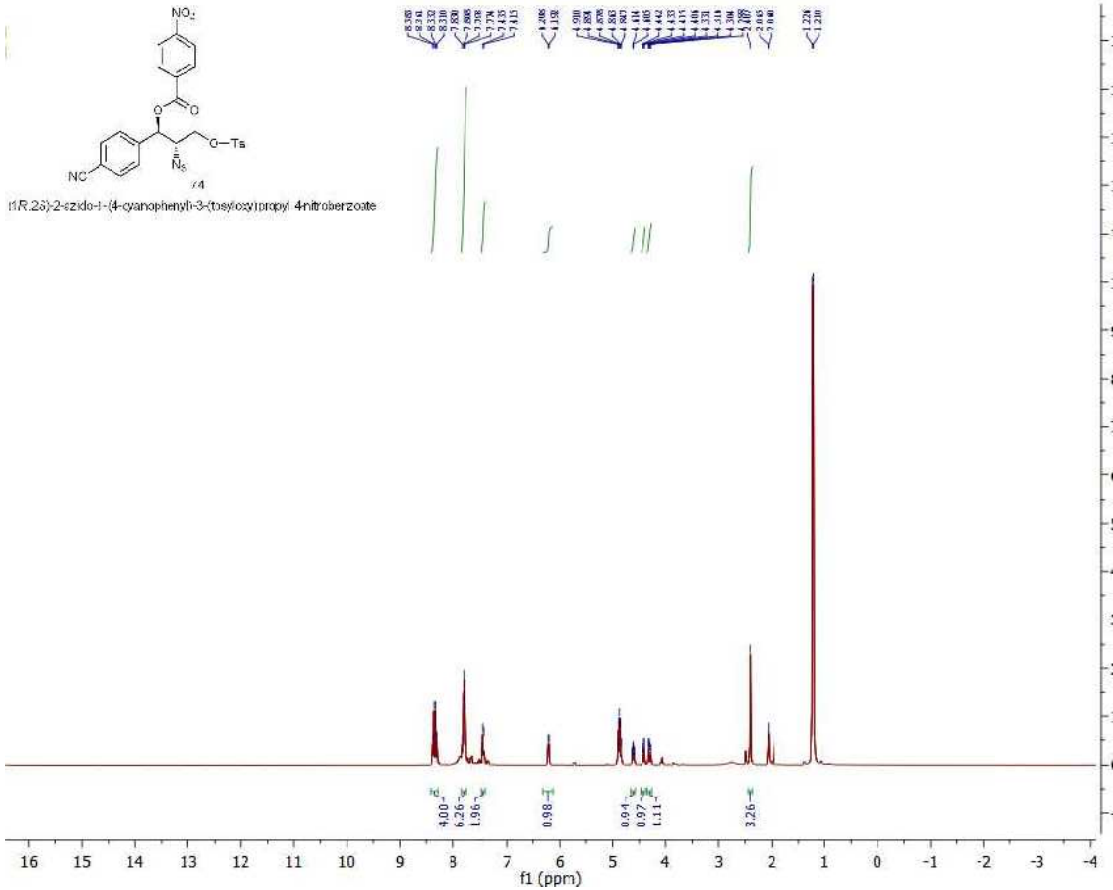
Parameters		
	Parameter	Value
1	Data File Name	G:\Data\Mitsunobu book 9 pg 79\1\fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	313.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	8
13	Receiver Gain	72
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1642.8
17	Nucleus	1H
18	Acquired Size	32768

^{1}H NMR (400 MHz, Acetone) δ 8.45 – 8.34 (m, 4H), 8.30 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.67 – 7.56 (m, 4H), 7.56 – 7.46 (m, 3H), 7.42 (d, *J* = 8.1 Hz, 2H), 6.11 (d, *J* = 6.7 Hz, 1H), 4.61 – 4.49 (m, 2H), 4.45 – 4.34 (m, 2H), 4.33 – 4.21 (m, 2H), 2.40 (s, 3H).



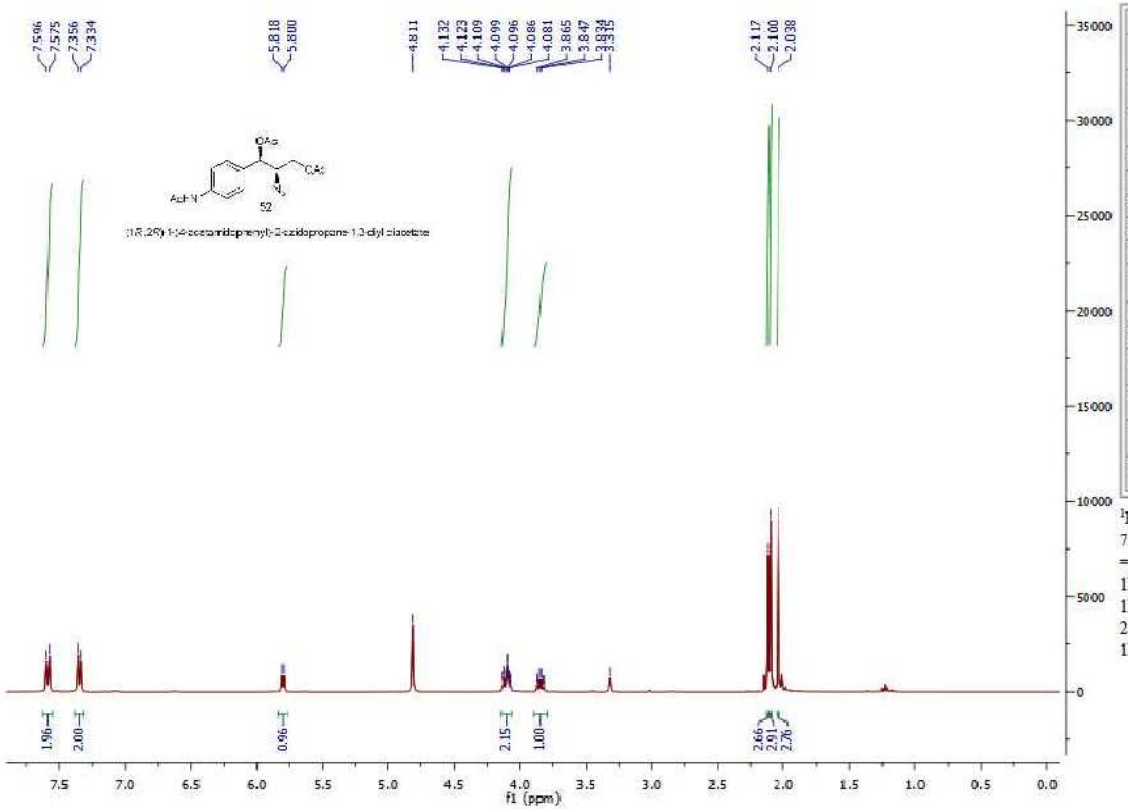
Parameters		
	Parameter	Value
1	Data File Name	G:\Data\Mitsunobu book 9 pg 79\2\fid
2	Title	
3	Comment	Bruker AV400 Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	vmbraga
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	313.2
10	Pulse Sequence	zgpg30
11	Experiment	1D
12	Number of Scans	512
13	Receiver Gain	32800
14	Spectrometer Frequency	100.62
15	Spectral Width	24038.5
16	Lowest Frequency	-3957.9
17	Nucleus	13C
18	Acquired Size	32768
19	Spectral Size	65536

^{13}C NMR (101 MHz, Acetone) δ 205.02, 162.86, 151.09, 145.41, 135.36, 134.70, 131.75, 131.68, 131.00, 130.04, 129.48, 129.42, 127.85, 123.70, 123.64, 122.61, 74.50, 68.10, 62.91, 29.43, 29.24, 29.05, 28.86, 28.66, 28.47, 28.28, 20.58.



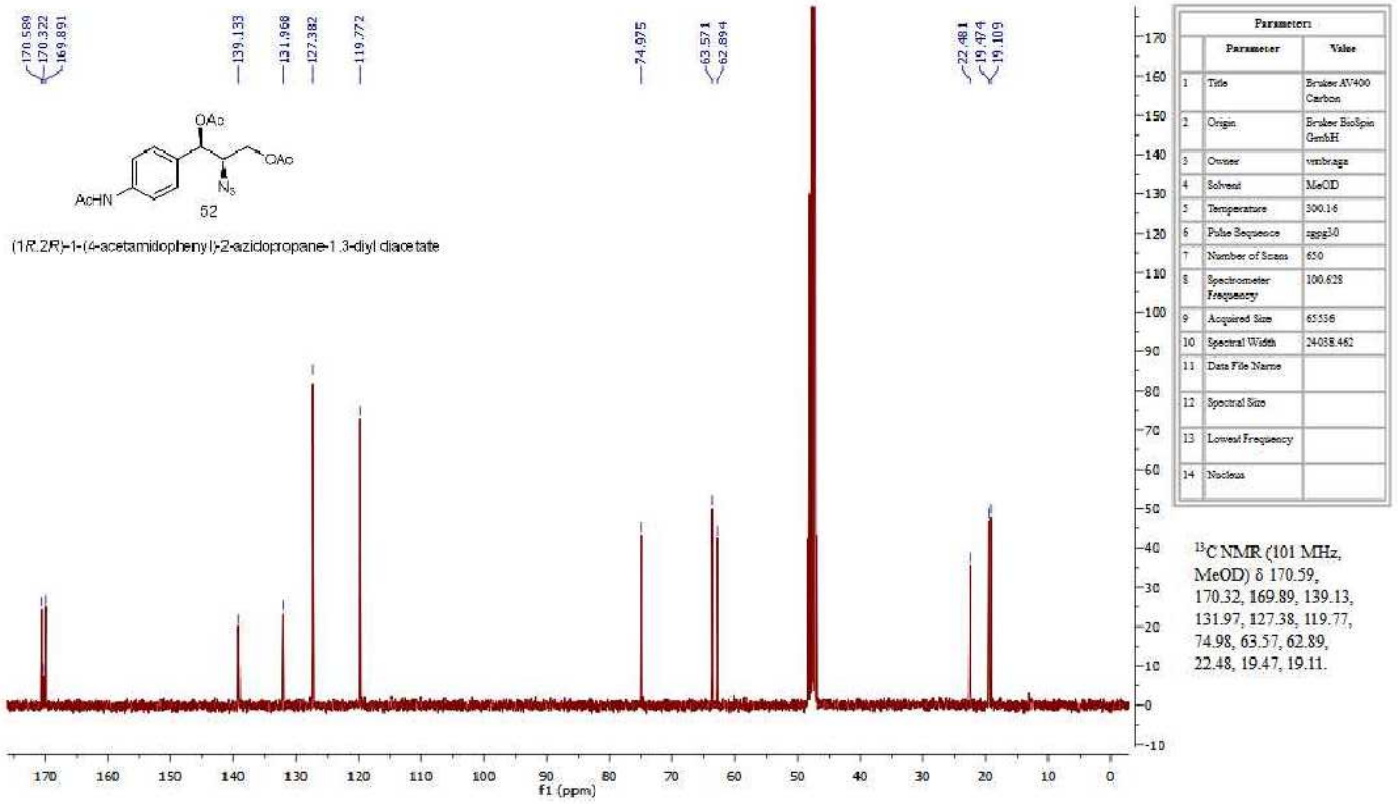
Parameters		
	Parameter	Value
1	DataFile Name	G:\ Data Mitsunobu \took 9 pg 77\ 1\ fid
2	Title	
3	Comment	Bruker AV400 Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	nmrsuage
6	Spectrometer	spect
7	Author	
8	Solvent	Acetone
9	Temperature	313.2
10	Pulse Sequence	zg30
11	Experiment	1D
12	Number of Scans	8
13	Receiver Gain	344
14	Spectrometer Frequency	400.15
15	Spectral Width	8223.7
16	Lowest Frequency	-1640.8
17	Nucleus	1H
18	Acquired Size	22760
19	Spectral Size	65536

^{1}H NMR (400 MHz, Acetone) δ 8.35 (dd, J = 20.3, 9.0 Hz, 4H), 7.80 (dd, J = 14.4, 8.2 Hz, 6H), 7.42 (d, J = 8.0 Hz, 2H), 6.20 (d, J = 6.7 Hz, 1H), 4.61 (td, J = 6.5, 3.5 Hz, 1H), 4.42 (dd, J = 10.9, 3.5 Hz, 1H), 4.31 (dd, J = 10.9, 6.3 Hz, 1H), 2.41 (s, 3H).



Parameters		
	Parameter	Value
1	Title	Bruker AV400 Proton
2	Origin	Bruker BioSpin GmbH
3	Owner	vmbraga
4	Solvent	MeOD
5	Temperature	300.16
6	Pulse Sequence	zg30
7	Number of Scans	8
8	Spectrometer Frequency	400.132
9	Acquired Size	65536
10	Spectral Width	8223.684
11	Data File Name	
12	Spectral Size	
13	Lowest Frequency	
14	Nucleus	

^{1}H NMR (400 MHz, MeOD) δ 7.59 (d, J = 8.5 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 5.81 (d, J = 7.3 Hz, 1H), 4.10 (dq, J = 5.4, 3.7 Hz, 1H), 3.84 (td, J = 7.5, 1.9 Hz, 1H), 2.12 (s, 1H), 2.10 (s, 2H), 2.04 (s, 1H).



Parameters		
	Parameter	Value
1	Title	Bruker AV400 Carbon
2	Origin	Bruker BioSpin GmbH
3	Owner	vmbraga
4	Solvent	MeOD
5	Temperature	300.16
6	Pulse Sequence	zgpg30
7	Number of Scans	650
8	Spectrometer Frequency	100.628
9	Acquired Size	65536
10	Spectral Width	24038.462
11	Data File Name	
12	Spectral Size	
13	Lowest Frequency	
14	Nucleus	

^{13}C NMR (101 MHz, MeOD) δ 170.59, 170.32, 169.89, 139.13, 131.97, 127.38, 119.77, 74.98, 63.57, 62.89, 22.48, 19.47, 19.11.

CHAPTER 7: VITA

Vanildo M. L. Braga was born in the city of Recife, state of Pernambuco, Brazil in September 10, 1973. His parents are Mr. Vanildo B. Vilela and Mrs. Evany M. Lima Braga. Vanildo earned a B.S in Chemical Engineering at Universidade Federal de Pernambuco, a M.Sc in Organic Chemistry in the same institution and a Ph.D in Pharmaceutical Sciences with emphasis in Medicinal Chemistry under the guidance of Dr. John M. Rimoldi in the Department of Medicinal Chemistry, School of Pharmacy of The University of Mississippi, U.S.A.